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Indole Syntheses Utilizing *o*-Methylphenyl Isocyanides

Yoshihiko Ito, Kazuhiro Kobayashi, Norihiko Seko, and Takeo Saegusa
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606
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New indole synthesis starting with *o*-methylphenyl isocyanides such as *o*-tolyl, 2,4-xylyl, and 2,6-xylyl isocyanide is described in full detail. Treatment of *o*-tolyl isocyanide with LDA in diglyme at −78 °C generated selectively *o*-(lithiomethyl)phenyl isocyanide in an almost quantitative yield, which on warming up to room temperature was cyclized to indole after aqueous workup. Similary, 2,4-xylyl and 2,6-xylyl isocyanides were cyclized to 5-methylindole and 7-methylindole quantitatively. The *o*-(lithiomethyl)phenyl isocyanides reacted with electrophiles such as alkyl halides and alkylene oxides to give *o*-alkylphenyl isocyanides, which were cyclized *via* the lithiation at the orthobenzylic carbon to afford 3-substituted indoles. On the other hand, the *o*-(lithiomethyl)phenyl isocyanides generated *in situ* at −78 °C was first warmed up to room temperature and then treated with electrophiles to furnish 1-substituted indoles. The *o*-(lithiomethyl)phenyl isocyanides were acylated in a fairly good yield with *N*-acylaziridines to give *o*-(acylmethyl)phenyl isocyanides, which were readily alkylated in the presence of sodium hydride to produce *o*-(1-acylalkyl)phenyl isocyanides. On acid hydrolysis followed by neutralization, *o*-(1-acylalkyl)phenyl isocyanides were converted to 2,3-disubstituted indoles.

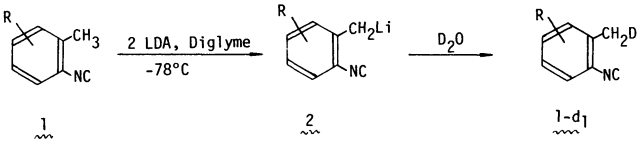
Since Schöllkopf[1] discovered the lithiation of isocyanides at the α-carbon, isocyanides have been useful and versatile reagents in organic syntheses.[2] The carbon-carbon bond formation with the α-metalated isocyanides provides a new methodology for nucleophilic introduction of masked α-aminoalkyl groups because the resulting isocyanides are readily converted to primary amine derivatives by acid hydrolysis.

On the other hand, isocyanide functional group itself, which may be regarded formally as carbene, has reacted with various polar reagents in an α-addition manner.[3] Isocyanides, which have no α-hydrogen, react with organolithium to afford lithiated aldimines, which are able to be used as acyl anion equivalents.[4]

The reactions of electrophiles with α-metalated isocyanides coupled with intramolecular α-addition to isocyanide carbon lead to the formation of heterocycles. The heterocycle syntheses have permitted rapid and efficient preparation of a variety of heterocyclic ring systems, which are otherwise accessible with difficulty.

On the background of isocyanide chemistry mentioned above, we have attempted a selective lithiation at the ortho-methyl group of *o*-tolyl isocyanide with the expectation that the resulting *o*-(lithiomethyl)-phenyl isocyanide might be cyclized by the intramolecular α-addition. In the preliminary paper,[5] we reported a successful selective lithiation at the ortho-methyl group of *o*-tolyl isocyanide and its intramolecular cyclization leading to indole. This paper describes the full scope of syntheses of indole derivatives by elaboration of *o*-(lithiomethyl)phenyl isocyanides. The selective lithiation and nucleophilic elaboration of *o*-methylphenyl isocyanides such as *o*-tolyl isocyanide 2,4- and 2,6-xylyl isocyanides, which are readily prepared from commercially available toluidine derivatives, make the present indole syntheses more flexible. The indole syntheses have many advantages of simplicity, versatility and high yields over the reported synthetic methods.[6]

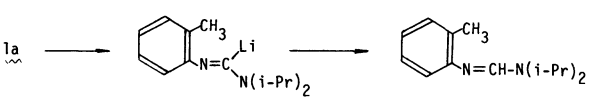
Selective Lithiation at the Benzylic Carbon of o-Alkylphenyl Isocyanides. Lithiation at the methyl group of *o*-tolyl isocyanide (**1a**) was achieved in an almost quantitative yield by treatment of **1a** with 2 equiv of lithium diisopropylamide (LDA) in diglyme at −78 °C. The deep-red *o*-(lithiomethyl)phenyl isocyanide (**2a**) thus generated was quenched at −78 °C with D_2O to yield *o*-tolyl isocyanide (>95% yield) with deuterium incorporation of >93%. The use of 2 equiv of LDA was required for the quantitative lithiation of **1a**. The silimar treatment of **1a** with 1 equiv of LDA followed by deuterolysis regenerated *o*-tolyl isocyanide (>95% yield) with deuterium incorporation of *ca.* 50%. The



1 2 1-d1

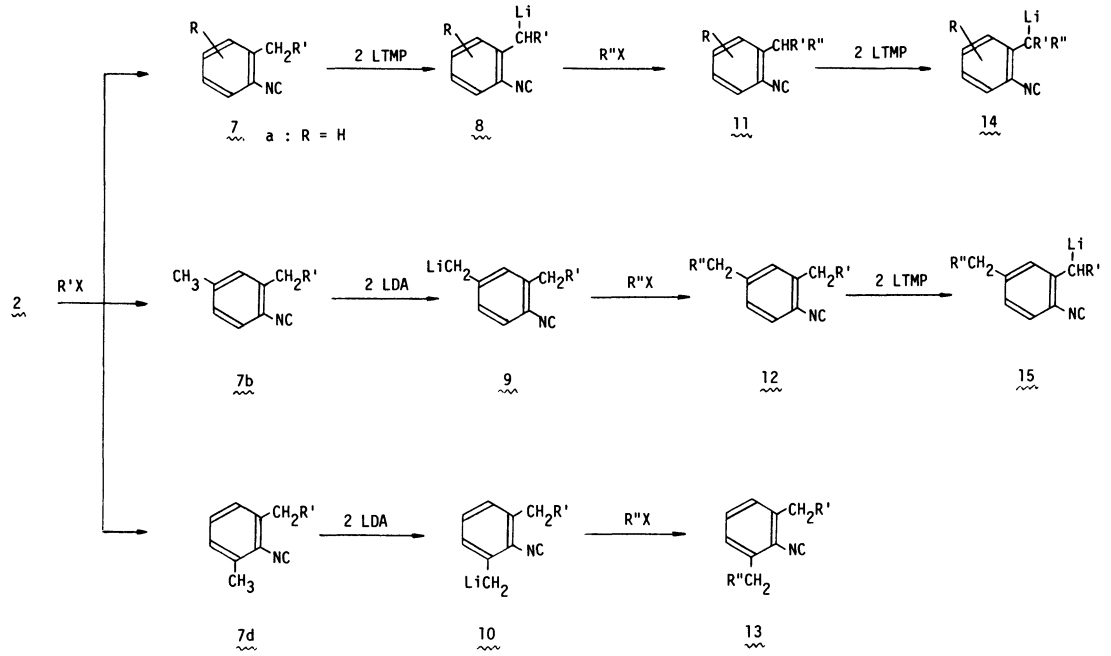
a : R = H
b : R = 4-Me
c : R = 5-Me
d : R = 6-Me
e : R = 4-MeO
f : R = 4-Cl

o-(lithiomethyl)phenyl isocyanide (**2a**) generated was stable at −78 °C under nitrogen in diglyme for several days. The selective lithiation of **1a** was solvent dependent. Use of monoglyme and heptane instead of diglyme gave **2a** but in somewhat decreased yields. In these solvents **2a** was slightly unstable and cyclized even at −78 °C within several hours, resulting in the formation of indole as mentioned later. The lithiation of **1a** in ether and THF solvents generated **2a** in a low yield, being substantially accompanied by an adduct (**3**) of LDA to the isocyano carbon of **1a**, of which hydrolysis furnished N^1,N^1-diisopropyl-N^2-(*o*-tolyl)formamidine (**4**). Similarly, the selective lithiation at the ortho-



3 4

methyl group of 2,4- (**1b**), 2,5- (**1c**), and 2,6-dimethylphenyl isocyanide (**1d**), 2-methyl-4-methoxyphenyl



Scheme 1.

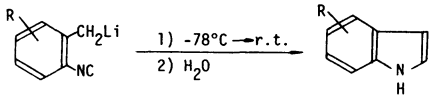
isocyanide (**1e**), and 2-methyl-4-chlorophenyl isocyanide (**1f**) was performed with 2 equiv of LDA in diglyme at −78 °C. The selective lithiation at the ortho-methyl group of **1b** may suggest that the lithiation at the ortho-methyl group of *o*-methylphenyl isocyanide (**1**) is assisted to some extent by the neighboring isocyano function. But, the treatment of **1b** and **1d** with 4 equiv of LDA in diglyme at −78 °C generated the respective dianions (**5**) and (**6**). Lithiation at the

ortho-benzylic carbon of *o*-alkylphenyl isocyanides (**7**), which are readily prepared by alkylations of **2**, can be selectively achieved by means of 2 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP). The benzylic lithiation of *o*-alkylphenyl isocyanides (**7**) with LDA was accompanied by an adduct of LDA onto the isocyano carbon of **7**. For instance, the treatment of *o*-pentylphenyl isocyanide (**7a-iii**) with LDA at −78 °C followed by warming up to room temperature produced, after aqueous workup, N^1, N^1-diisopropyl-N^2-(*o*-pentylphenyl)formamidine (60%) and 3-butylindole (30%), which is formed by the intramolecular cyclization of *o*-(α-lithiopentyl)phenyl isocyanide (**8a-iii**).

Noteworthy is that the lithiation of 2-alkyl-4-methylphenyl isocyanide (**7b**) and 2-alkyl-6-methylphenyl isocyanide (**7d**) with 2 equiv of LDA took place selectively at the 4-methyl and the 6-methyl groups, respectively, leading to 2,4-dialkylphenyl isocyanide (**12**) and 2,6-dialkylphenyl isocyanide (**13**) by alkylations (Scheme 1).

As expectedly, further lithiation of 2,4-dialkylphenyl isocyanides (**12**) with 2 equiv of LTMP occurred at the ortho-benzylic carbon with high selectivities.

Alkylations and Cyclizations of o-Alkylphenyl Isocyanides via the Selective Lithiation at the ortho-Benzylic Carbon. i) Syntheses of 3-Alkylindoles: *o*-(Lithiomethyl)phenyl isocyanide (**2a**), which is stable at −78 °C in diglyme, was cyclized on warming to give indole, after aqueous workup. Deep red characteristic of **2a** in diglyme at −78 °C gradually turned light brown as the temperature was raised up above −25 °C to room temperature. The light brown solution was quenched with H_2O at room temperature to produce indole in an almost quantitative yield. Similarly, the cyclizations of substituted *o*-methylphenyl isocyanides (**1b**—**f**) *via* the lithiation at the ortho-methyl group afforded indoles with substituents on the benzene ring in high yields.

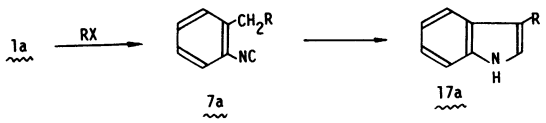


2	**16**
a : R = H	a : 100%
b : R = 4-Me	b : 100%
c : R = 5-Me	c : 82%
d : R = 6-Me	d : 100%
e : R = 4-MeO	e : 91%
f : R = 4-Cl	f : 100%

The *o*-(lithiomethyl)phenyl isocyanides can be elaborated at −78 °C with electrophiles such as alkyl halides, aldehydes,[7] ketones,[7] epoxides, α, β-unsaturated carboxylic esters,[8] allyl carboxylates,[9] *N*-acylaziridines *etc.*, leading to a variety of *o*-substituted phenyl isocyanides. Some alkylations of *o*-(lithiomethyl)phenyl isocyanide (**2a**) including silylation and sulfenylation are summarized in Table 1.

The reactions of **2a** with alkyl halides are immedi-

Table 1. Alkylations and cyclizations of *o*-tolyl isocyanide (**1a**)



Entry	RX[a]	**7a** (%)	**17a**[b] (%)
1	CH_3I	95 (**7a-i**)	95 (**17a-i**)
2	CH_2=$CHCH_2Br$	82 (**7a-ii**)	95 (**17a-ii**)
3	*n*-C_4H_9Br	83 (**7a-iii**)	85 (**17a-iii**)
4	*i*-C_4H_9Br	78 (**7a-iv**)	78 (**17a-iv**)
5	*i*-C_3H_7I	89 (**7a-v**)	65 (**17a-v**)
6	$(EtO)_2CHCH_2Br$	68 (**7a-vi**)	62 (**17a-vi**)
7	Me_3SiCl	95 (**7a-vii**)	90 (**17a-vii**)
8	MeSSMe[c]	67 (**7a-viii**)	84 (**17a-viii**)

a) Two equivalents of electrophile was used unless otherwise stated. b) Isolated yields from **7a**. c) One equivalent of electrophile was used.

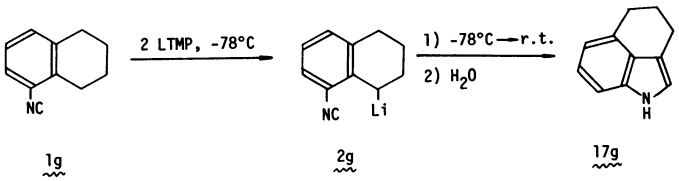
ately complete at −78 °C except for that **2a** reacted slowly with α-bromoacetaldehyde diethy acetal at −78 °C over 8—10 h. The reactions of **2a** with trimethylsilyl chloride and dimethyl disulfide permitted introductions of trimethylsilyl and methanesulfenyl groups on the methyl group of *o*-tolyl isocyanide (**1a**), both of which in turn are capable of stabilizing benzylic carbanion.

o-Alkylphenyl isocyanides (**7a-i**—**7a-iv** and **7a-vi**) thus prepared were cyclized to 3-substituted indoles in good yields by the selective lithiation at the ortho-benzylic carbon with 2 equiv of LTMP at −78 °C followed by raising the reaction temperature. Some syntheses of 3-alkylindoles (**17a**) are summarized in Table 1.

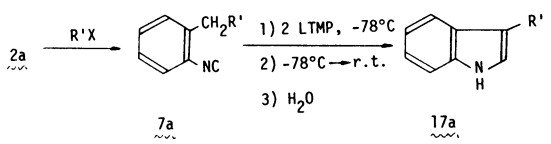
The cyclization of **7a-vi** presents a convenient synthesis of diethyl acetal (**17a-vi**) of indole-3-acetaldehyde, which is a metabolite from Helianthus Annuus. No cyclization of **7a-v** occurred on the similar treatment, because of the failure in the lithiation at the benzylic carbon with LTMP. Its cyclization was realized by successful lithiation at the ortho-benzylic carbon of **7a-v** with LTMP in the presence of HMPA. Cyclizations of **7a-vii** and **7a-viii**, of which the benzylic carbanions are stabilized by silicon and sulfur atoms, are readily accomplished *via* the lithiation with LDA.

All attempts to synthesize 3-alkylindoles (**17a**) in one-flask *via* alkylation and cyclization starting with *o*-methylphenyl isocyanide (**1a**) were, however, unsuccessful.

The present methodology also provides a convenient synthetic route to 1,3,4,5-tetrahydrobenz[*cd*]indole (**17g**), which constitutes the skeleton of ergot alkaloid, from 5,6,7,8-tetrahydro-1-naphthylamine *via* the lithiation of the corresponding isonitrile (**1g**) with LTMP as shown below.



The alkylation and cyclization using 2,4- and 2,6-dimethylphenyl isocyanides (**1b**) and (**1d**) make the present indole syntheses more applicable. 2,4-Dialkylphenyl isocyanides (**12**) were prepared *via* the stepwise selective lithiation (**2b** and **9**) or the direct lithiation (**5**) of **1b**, followed by alkylations. The 2,4-dialkylphenyl isocyanides (**12**) were cyclized *via* the selective lithiation at the ortho-benzylic carbon with 2 equiv of LTMP to 3,5-dialkylindoles (**18**) but in somewhat low yields.



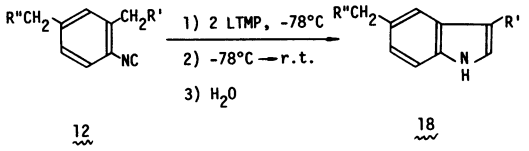
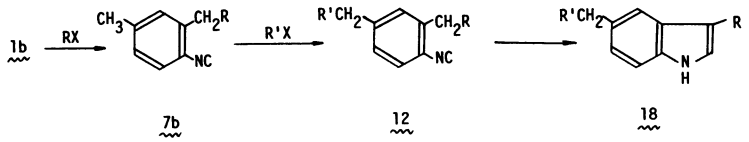


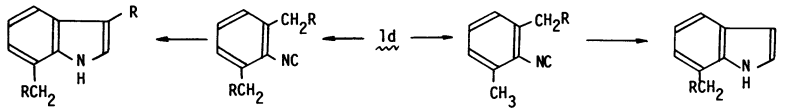
Table 2. Alkylations and cyclizations of 2,4-dimethylphenyl isocyanides (**1b**)



Entry	RX	R'X	**7b** (%)[a]	**12** (%)[a]	**18** (%)[d]
1	CH_3I	—	93 (**7b-i**)		
2	*n*-C_4H_9Br	—	99 (**7b-ii**)		
3	CH_2=$CHCH_2Br$	—	98 (**7b-iii**)		
4	CH_3I	CH_3I		78[b] (64)[c] (**12-i**)	39 (**18-i**)
5	*n*-C_4H_9Br	*n*-C_4H_9Br		79[b] (75)[c] (**12-ii**)	30 (**18-ii**)
6	*n*-C_4H_9Br	CH_2=$CHCH_2Br$		86[b] (**12-iii**)	40 (**18-iii**)
7	CH_2=$CHCH_2Br$	*i*-C_3H_7I		69[b] (**12-iv**)	47 (**18-iv**)

a) Yields based on **1b**. b) Yields are of stepwise alkylation *via* **7b**. c) Yields in parenthesis are of dialkylation *via* the direct dilithiation (**5**). d) Yields based on **12**.

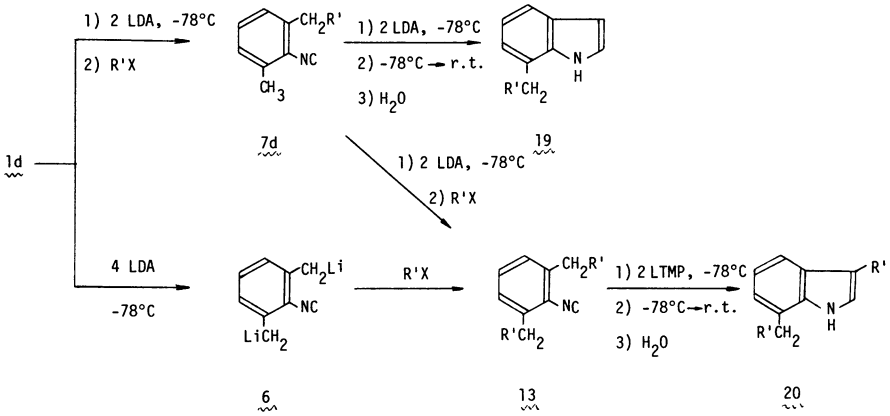
Table 3. Alkylations and cyclizations of 2,6-dimethylphenyl isocyanides (**1d**)



20 **13** **7d** **19**

Entry	RX	**7d** (%)[a]	**13** (%)[a]	**19** (%)[d]	**20** (%)[e]
1	n-C_4H_9Br	87 (**7d-i**)		66 (**19-i**)	
2	i-C_3H_7I	75 (**7d-ii**)		74 (**19-ii**)	
3	n-C_4H_9Br		60[b] (70)[c] (**13-i**)		43 (**20-i**)
4	CH_3I		75[b] (**13-ii**)		63 (**20-ii**)

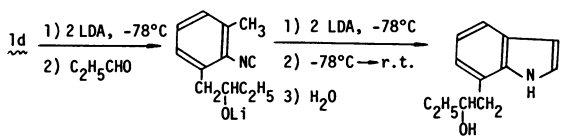
a) Yields based on **1d**. b) Yields are of the direct alkylation *via* **6**. c) Yields in parenthesis is of the stepwise alkylation *via* **10**. d) Yields based on **7d**. e) Yields based on **13**.



Scheme 2.

Similarly, mono- and dialkylations of 2,6-dimethylphenyl isocyanide (**1d**) were carried out *via* the stepwise selective lithiation (**2d** and **10**) or the direct lithiation (**6**). The monoalkylations of **1d** and subsequent cyclizations *via* the selective lithiation at the remaining methyl group provided a convenient synthesis of 7-alkylindoles (**19**) (Table 3).

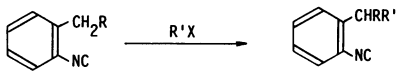
2,6-Dialkylphenyl isocyanides (**13**) were also cyclized to 3,7-dialkylindoles (**20**) *via* the benzylic lithiation with LTMP (Table 3). But the cyclization of unsymmetrical 2,6-dialkylphenyl isocyanide was less significant from synthetic viewpoint, because of difficulty in the selective lithiation at either of two ortho-benzylic carbons. Another interesting elaboration of **1d** *via* **21** is illustrated in preparation of **19-iii**.



21 **19-iii**

o-Alkylphenyl isocyanides **7a** were further alkylated by treatment with 2 equiv of lithium amide followed by addition of alkyl halides to afford *o*-(*s*-alkyl)phenyl isocyanides (**22**) in moderate to good yields (Table 4). Various attempts to cyclize *o*-(*s*-alkyl)phenyl isocyanides (**22**) to indolenine derivatives (**23**), however, failed, in spite of success of the benzylic lithiation.[10]

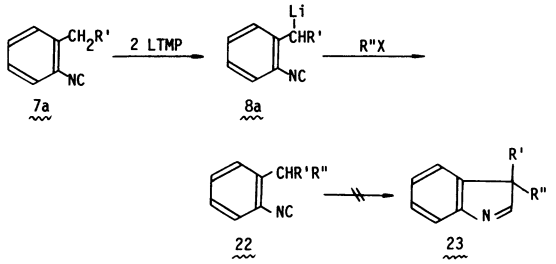
Table 4. Alkylations of **7a**[a]



7a **22**

Entry	R	R'X	**22** (%)
1	CH_3	n-C_4H_9Br	72 (**22-i**)
2	n-C_4H_9	CH_3I	66 (**22-i**)
3	CH_3	CH_3I	68 (**22-ii**)
4	CH_3	CH_3SSCH_3	75 (**22-iii**)
5	SCH_3[b]	CH_3I	78 (**22-iii**)
6	SCH_3[b]	CH_3SSCH_3	65 (**22-iv**)
7	$Si(CH_3)_3$[b]	CH_3I	88 (**22-v**)

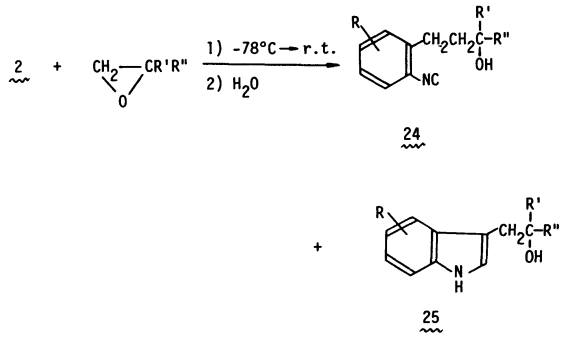
a) LTMP was used for the ortho-benzylic lithiation of **7a** unless otherwise noted. b) LDA was used for the ortho-benzylic lithiation.



7a **8a** **22** **23**

ii) One-flask Synthesis of Tryptophol Derivatives: The carbon-carbon bond formation of *o*-(lithiomethyl)-phenyl isocyanides (**2**) with alkylene oxide and subsequent cyclization of the resultant *o*-(3-hydroxyalkyl)-phenyl isocyanide (**24**) *via* the ortho-benzylic lithiation provided a rapid synthetic route to tryptophol derivatives.

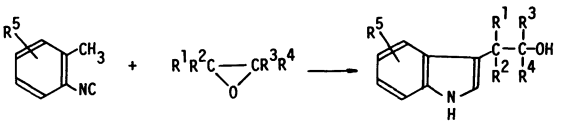
Unlike the synthesis of 3-alkylindoles by the alkylation and cyclization of **1** as mentioned above, the synthesis of tryptophol derivatives starting with *o*-methylphenyl isocyanides (**1**) was accomplished in one-flask without isolation of any intermediates. In the reaction of **2a** generated *in situ* from **1a** and 2 equiv of LDA at −78 °C in diglyme with 2 equiv molar of alkylene oxide for 2 h, *o*-(3-hydroxyalkyl)phenyl isocyanide (**24**) was produced together with tryptophol derivatives (**25**) as a minor product, after aqueous workup at room temperature. The formation of **25** suggested



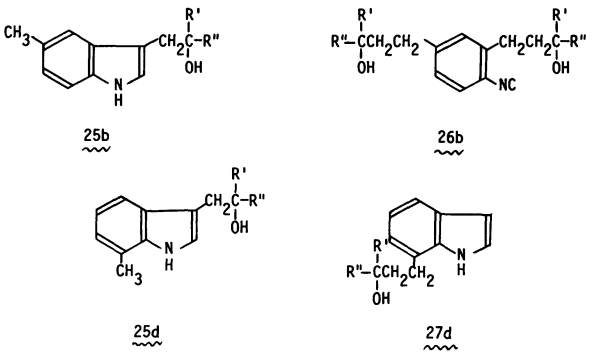
that lithium alkoxide of **24** initially formed from **2** and alkylene oxide underwent the ortho-benzylic lithiation with LDA during the reaction. Expectedly, *o*-(3-hydroxyalkyl)phenyl isocyanide (**24**) once isolated was converted to tryptophol derivative *via* the ortho-benzylic lithiation by 3 equiv of LDA. In this case, use of LTMP was not necessary. On the basis of these observations, one-flask synthesis of tryptophol derivatives was realized as follows. To the mixture of **1** and 2 equiv of LDA, which had been stirred at −78°C for 3 h, another 2 equiv of LDA was added at the same temperature and stirred for 2 h. The reaction mixture was warmed up to room temperature and quenched with water to furnish tryptophol derivative (**25**) in moderate yields. With unsymmetrical alkylene oxides, isomeric tryptophol derivatives, which may be derived by nucleophilic attack of **2** at the more substituted site of alkylene oxides, was produced in negligible yields as a by-product as judged by NMR analysis. Some syntheses of tryptophol derivatives starting with **1** are summarized in Table 5.

The tryptophol syntheses with 2,4- and 2,6-dimethylphenyl isocyanide (**1b**) and(**1d**) were accompanied by side reactions, which were caused from the lithiation at 4-methyl and 6-methyl of 2-(3-hydroxyalkyl)-4-methylphenyl isocyanide and 2-(3-hydroxyalkyl)-6-methylphenyl isocyanide. Accordingly, 2,4-bis(3-hydroxyalkyl)phenyl isocyanide (**26b**) and 7-(3-hydroxyalkyl)-indole (**27d**) were isolated with the desired tryptophol derivatives (**25b**) and (**25d**), respectively.

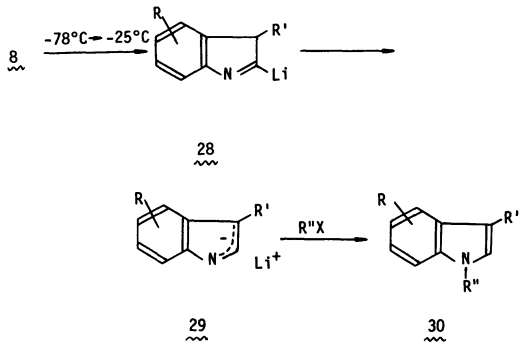
Table 5. One-flask synthesis of tryptophol derivatives (**25**)



Entry	R^1	R^2	R^3	R^4	R^5		Yield/%
1	H	H	CH_3	CH_3	H	(**25a-i**)	68
2	H	H	H	C_2H_5	H	(**25a-ii**)	61
3	H	H	H	CH_3	H	(**25a-iii**)	65
4	H	$-(CH_2)_4-$			H	(**25a-iv**)	42
5	H	H	CH_3	CH_3	5-CH_3	(**25b-v**)	48
6	H	H	H	CH_3	5-CH_3	(**25b-vi**)	48
7	H	H	CH_3	CH_3	7-CH_3	(**25d-vii**)	23
8	H	H	CH_3	CH_3	5-Cl	(**25e-viii**)	78

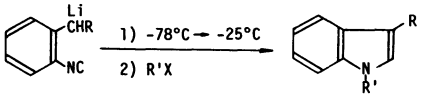


iii) Syntheses of 1-Alkylinodoles: The present indole synthesis presents an interesting example of a "5-*endo*-digonal" ring closure as classified by Baldwin,[11] in which the benzylic carbanion **8**, adds intramolecularly to the adjacent isocyano carbon, resulting in the formation of lithiated aldimine derivative (**28**). Attempts to

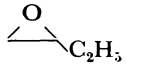
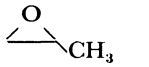
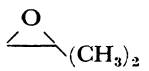
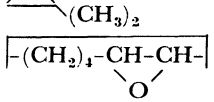


trap the lithiated aldimine **28** with electrophiles which could provide an entry to 2-substituted indoles, were, however, unsuccessful. When **8** generated *in situ* in diglyme at −78 °C was allowed to warm up to −25 °C, the characteristic color of **8** (R=H: deep red; R=alkyl: purple) gradually changed to light brown. The solution at −25 °C was treated with electrophiles such as alkyl halides, alkylene oxides, *etc.*, to afford the corresponding 1-substituted indoles (**30**) in good yields

Table 6. Synthesis of 1-substituted indoles

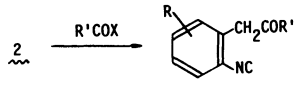


8a 30a

Entry	R	R'X	**30a** (%)[a]
1	H	CH_3I	82 (**30a-i**)
2	H	n-C_4H_9Br	82 (**30a-ii**)
3	H	CH_3OCOCH_2Br	52 (**30a-iii**)
4	H	$(CH_3)_3SiCl$	87 (**30a-iv**)
5	H	C_2H_5COCl	79 (**30a-v**)
6	H	CH_3OCOCl	76 (**30a-vi**)
7	H		84 (**30a-vii**)[b]
8	H		72 (**30a-viii**)[b]
9	H		65 (**30a-ix**)[b]
10	H		18 (**30a-x**)
11	CH_3	n-C_4H_9Br	65 (**30a-xi**)

a) Yields based on **7a**. b) Isomeric 1-(2-hydroxyalkyl)-indoles, which may be formed by nucleophilic attack of **29** at the more substituted carbon of alkylene oxide, were produced in negligible yields.

Table 7. Acylations of **2**



31

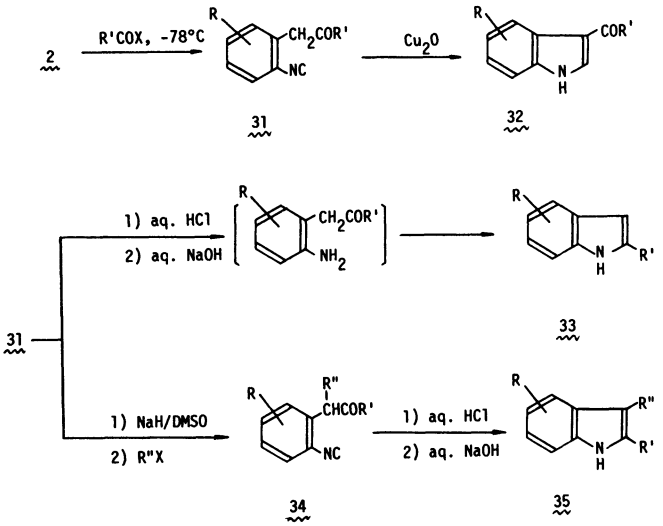
Entry	R	R'	**31** (%)[a]
1	H	CH_3	92 (**31-i**)[b]
2	H	t-C_4H_9	86 (**31-ii**)[b]
3	H	$Cl(CH_2)_3$	52 (**31-iii**)[c]
4	H	$HO(CH_2)_3$	47 (**31-iv**)[d]
5	4-CH_3	t-C_4H_9	85 (**31-v**)[b]
6	6-CH_3	t-C_4H_9	80 (**31-vi**)[b]

a) Ref. 9. b) The corresponding N-acylaziridine was used. c) Ethyl 4-chlorobutyrate was used. d) γ-Butyrolactone was used.

(Table 6). The observation indicates that the lithiated aldimine **28** was rapidly converted to **29** even at −25 °C. Consequently, this procedure provided a convenient synthetic method of 1-substituted indoles starting with o-methylphenyl isocyanides (**1**).

Acylations and Cyclizations of o-Methylphenyl Isocyanides. Syntheses of 2,3-Disubstituted Indoles: Unlike the alkoxycarbonylation[4] of **2** with chloroformate, acylation of **2** was not successful with acyl halides. Carboxylic esters were conveniently employed for the acylations of **2** to afford o-(acylmethyl)-phenyl isocyanides (**31**). Allyl carboxylates gave better yields, but alkyl carboxylates including γ-butyrolactone were also usable. High-yielding acylations of **2** were accomplished with N-acylaziridines, as listed in Table 7.

As already reported,[9] 2-(acylmethyl)phenyl isocyanides (**31**) thus prepared were useful synthetic intermediates, which were cyclized to 3-acylindoles (**32**) by a Cu_2O catalyst and to 2-alkylindoles (**33**) on acid hydrolysis followed by neutralization. Usefulness of



31 was further demonstrated by cyclization coupled with alkylation of **31**, producing 2,3-disubstituted indoles (**35**). Alkylations of **31** having an active methylene group were conducted more easily by means of NaH, producing 2-(1-acylalkyl)phenyl isocyanides (**34**). (Table 8) The isocyanides **34** prepared were unexpectedly not cyclized by Cu_2O catalyst.[9] Moreover, **34-i** was treated with NaH at −78 °C followed by warming up to room temperature to give 3-methylindole and 1-acetyl-3-methylindole in good yield. But, **34** was cleanly converted to 2,3-disubstituted indole (Table 8) in good yield on treatment with aqueous HCl. This reaction presents an expedient and versatile preparative method of 2,3-disubstituted indoles.

Experimental

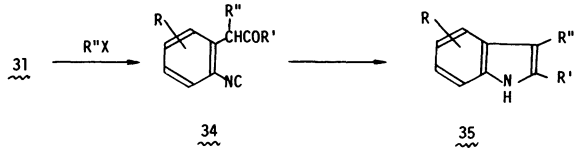
Measurements. The ^1H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard, unless otherwise stated. The IR spectra were measured of neat samples, unless otherwise stated. Thin layer chromatography was performed using Merck Silica Gel 60 GF_{254}.

Materials. All solvents were dried over drying agents and distilled under nitrogen. Butyllithium (1.6 M† solution in hexane) was purchased from aldrich Inc. Alkyl halides and alkylene oxides were all purified by distillation under nitrogen. Starting o-methylphenyl isocyanides (**1a—f**) were prepared according to the Ugi's procedure[12] or the modified procedure (*vide infra*) from the corresponding formamides, which were prepared by formylation of commercially available o-toluidines with formic acid or acetic formic anhydrid.[13]

5-Isocyano-1,2,3,4-tetrahydronaphthalene (1g). To a solution of 6.0 g (34 mmol) of 5-formamido-1,2,3,4-tetra-

† 1 M=1 mol dm^{-3}.

Table 8. Alkylations and cyclizations of **31**



Entry	R	R′	R″X	**34** (%)[a]	**35** (%)[b]
1	H	CH_3	CH_3I	84 (**34-i**)	62 (**35-i**)
2	H	i-C_4H_9	CH_3I	90 (**34-ii**)	77 (**35-ii**)
3	H	t-C_4H_9	CH_3I	85 (**34-iii**)	86 (**35-iii**)
4	H	t-C_4H_9	i-C_3H_7I	63 (**34-iv**)	90 (**35-iv**)
5	H	t-C_4H_9	CH_3COCH_2Br	56 (**34-v**)	59 (**35-v**)
6	H	t-C_4H_9	$NCCH_2I$	89 (**34-vi**)	75 (**35-vi**)
7	H	Ph	CH_2=$CHCHBr$	70 (**34-vii**)	66 (**35-vii**)
8	4-CH_3	t-C_4H_9	$C_2H_5OCOCH_2Br$	77 (**34-viii**)	46 (**35-viii**)
9	6-CH_3	t-C_4H_9	CH_2=$CHCH_2Br$	78 (**34-ix**)	67 (**35-ix**)
10	H	$Cl(CH_2)_3$	R″=H	—	55 (**33-i**)
11	H	$HO(CH_2)_3$	R″=H	—	53 (**33-ii**)

a) Isolated yield based on **31**. b) Isolated yield based on **34**.

hydronaphthalene, which was prepared from 5,6,7,8-tetrahydro-1-naphthylamine[14] and formic acid, and 14 mL of triethylamine in 40 mL of THF, was added dropwise 5.2 g (34 mmol) of phosphoryl chloride at 0 °C. After stirring at the same temperature for 30 min, the mixture was stirred for additional 30 min at room temperature, and poured into diluted aq $NaHCO_3$, extracted with ether and washed with water. The extract was dried over KOH pellet, filtered and evaporated. The residue was distilled to afford 4.7 g (88%) of 5-isocyano-1,2,3,4-tetrahydronaphthalene (**1g**), bp 86—87 °C (0.4 mmHg[††]). **1g**: IR 2110 cm^{-1}; NMR δ=1.55—2.10 (m, 4H), 2.46—3.10 (m, 4H), 6.75—7.30 (m, 3H). Found: C, 83.90; H, 7.21; N, 9.11%. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91%.

*5-Methylindole (**16b**).* *General Procedure*: To a solution of 304 mg (3 mmol) of diisopropylamine in 4 mL of diglyme was added dropwise 3 mmol of butyllithium (1.6 M solution in hexane) at −78 °C, and stirred for 15 min at the same temperature. To the mixture, 197 mg (1.5 mmol) of 2,4-xylyl isocyanide (**1b**) was added and stirred for 30 min at −78 °C. The resultant red solution was allowed to warm up to room temperature, and quenched with aq NH_4Cl. The mixture was extracted with ether, washed with water three times and dried over anhydrous Na_2SO_4. After the ether extract was evaporated, the residual solid was recrystallized from hexane to furnish 5-methylindole in an almost quantitative yield, mp 57 °C (lit,[6d] 55.0—56.5 °C). IR (KBr disk) 3400 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=2.36 (s, 3H), 6.22 (m, 1H), 6.61 (m, 1H), 6.83 (br s, 2H), 7.0 (br s, 1H), 7.22 (br s, 1H).

Indole (**16a**),[15a] 6-methylindole (**16c**),[16] 7-methylindole (**16d**),[15b] 5-methoxyindole (**16e**),[15c] and 5-chloroindole (**16f**)[15d] were synthesized according to the above procedure, and purified by recrystallization from hexane except for **16c** which was distilled, bp 60 °C (0.2 mmHg) [lit,[16] 148—155 °C (20 mmHg)]. Identities of **16a—f** were established by comparison of their spectral data with those reported. **16c**: IR 3400 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=2.42 (s, 3H), 6.31 (m, 1H), 6.7—7.5 (m, 5H).

*o-Ethylphenyl Isocyanide (**7a-i**).* *General Procedure for Alkylations of o-Tolyl Isocyanide (**1a**)*: To a stirring solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added dropwise 176 mg (1.5 mmol) of *o*-tolyl isocyanide (**1a**). After 30 min, 426 mg (3 mmol) of methyl iodide was added dropwise. The characteristic red color of *o*-(lithiomethyl)-phenyl isocyanide (**2a**) disappeared immediately. The reaction mixture was quenched with aq NH_4Cl at −78 °C, extracted with ether, washed with water three times and dried over anhydrous Na_2SO_4. The ether extract was evaporated and distilled using Kugelrohr apparatus to afford *o*-ethylphenyl isocyanide (**7a-i**) [bp 85 °C (10 mmHg)] in 95% yield. **7a-i**: IR 2115 cm^{-1}; NMR δ=1.28 (t, 3H), 2.77 (q, 2H), 7.20 (s, 4H). Found: C, 82.62; H, 7.09; N, 10.85%. Calcd for C_9H_9N: C, 82.40; H, 6.92; N, 10.68%. *o*-Alkylphenyl isocyanides (**7a-ii**)—(**7a-viii**) were prepared according to the above procedure.

*o-(3-Butenyl)phenyl Isocyanide (**7a-ii**)*: [Bp 70 °C (1 mmHg)]: IR 2120, 1641 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=2.40 (t, 2H), 2.6—3.0 (m, 2H), 4.8—5.2 (m, 2H), 5.5—6.0 (m, 1H), 7.0—7.5 (m, 4H). Found: C, 84.19; H, 7.20; N, 9.01%. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91%.

*o-Pentylphenyl Isocyanide (**7a-iii**)*: [Bp 85 °C (4 mmHg)]: 2120 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=0.95 (t, 3H), 1.1—1.8 (m, 6H), 2.72 (t, 2H), 7.16 (s, 4H). Found: C, 83.45; H, 8.90; N, 8.04%. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09%.

*o-Isopentylphenyl Isocyanide (**7a-iv**)*: [Bp 86 °C (5 mmHg)]: IR 2110 cm^{-1}; NMR δ=0.95 (d, 6H), 1.3—1.7 (m, 3H), 2.72 (t, 2H), 7.23 (s, 4H). Found: C, 83.01; N, 8.89; N, 8.32%. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09%.

*o-Isobutylphenyl Isocyanide (**7a-v**)*: [Bp 80 °C (4 mmHg)]: IR 2115 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=0.94 (d, 6H), 1.95 (m, 1H), 2.58 (d, 2H), 7.19 (s, 4H). Found: C, 83.01; H, 8.50; N, 8.66%. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80%.

*o-(3,3-Diethoxypropyl)phenyl Isocyanide (**7a-vi**)*: [Bp 120 °C (0.8 mmHg)]: The reaction of *o*-(lithiomethyl)phenyl isocyanide (**2a**) with bromoacetaldehyde diethyl acetal was slow at −78 °C and took about 10 h before the red color of **2a** diasppeared. IR 2115 cm^{-1}; NMR(CCl_4 with Me_4Si) δ= 1.19 (t, 6H), 1.7—2.1 (m, 2H), 2.6—2.9 (m, 2H), 3.2—3.7 (m, 4H), 4.3—4.6 (m, 1H), 7.20 (s, 4H). Found: C, 71.98; H, 8.34; N, 5.79%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%.

†† 1 mmHg≈133.322 Pa.

*o-(Trimethylsilylmethyl)phenyl Isocyanide (**7a-vii**)*: [Bp 105 °C (4 mmHg)]: IR 2130, 1252, 852 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=−0.06 (s, 9H), 2.15 (s, 2H), 6.7—7.2 (m, 4H). Found: C, 69.54; H, 7.74; N, 7.40%. Calcd for $C_{11}H_{15}NSi$: C, 69.78; H, 7.99; N, 7.40%.

*o-(Methylthiomethyl)phenyl Isocyanide (**7a-viii**)*: [Bp °C (1 mmHg)]: IR 2115 cm^{-1}; NMR(CCl_4 with Me_4Si) δ= 1.97 (s, 3H), 3.69 (s, 2H), 7.1—7.4 (m, 4H). Found: C, 66.41; H, 5.31; N, 8.60%. Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58%.

*3-Methylindole (**17a-i**). General Procedure for Preparation of 3-Alkylindoles*: To a solution of 424 mg (3 mmol) of 2,2,6,6-tetramethylpiperidine in 4 mL of diglyme was added dropwise 3 mmol of butyllithium (1.6 M solution in hexane) at −78 °C, and stirred for 15 min at the same temperature. To the mixture, 197 mg (1.5 mmol) of *o*-ethylphenyl isocyanide (**7a-i**) was added and stirred for 30 min at −78 °C. The purple solution was then allowed to warm up to room temperature and quenched with aq NH_4Cl. The mixture was worked up in the same way mentioned for the preparation of **16b**. 3-Methylindole (**17a-i**) was recrystallized from hexane (95% yield) and identified by comparison of spectral data[15e] with those of the authentic sample.

3-Alkylindoles (**17a-ii**)—(**17a-vi**) and (**17g**) were prepared from the corresponding **7** according to the above procedure.

*3-Allylindole (**17a-ii**)*:[17] TLC(Silica gel, $CHCl_3$) R_f=0.79.

*3-Butylindole (**17a-viii**)*:[18] [Bp 130 °C (1 mmHg)]: IR 3400 cm^{-1}; NMR δ=0.93 (t, 3H), 1.1—1.8 (m, 4H), 2.72 (t, 2H), 6.9—7.6 (m, 5H), 7.9 (br 1H).

*3-Isobutylindole (**17a-iv**)*: [Mp 32 °C recrystallization from hexane (lit,[19] 31—32 °C)]: IR 3400 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=0.96 (d, 6H), 1.96 (m, 1H), 2.61 (d, 2H), 6.86 (m, 1H), 7.0—7.3 (m, 3H), 7.5—7.7 (m, 1H), 7.9 (br 1H).

*Indole-3-acetaldehyde Diethyl Acetal (**17a-vi**)*: [Bp 140 °C (0.4 mmHg)]: IR 3400 cm^{-1}; NMR(CCl_4 with Me_4Si) δ= 1.09 (t, 6H), 2.90 (d, 2H), 3.39 (m, 4H), 4.63 (t, 1H), 6.7—6.9 (m, 4H), 7.2—7.5 (m, 1H), 8.0—8.2 (br 1H). Found: C, 72.33; H, 8.11; N, 6.23%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%.

1,3,4,5-Tetrahydrobenz[cd]*indole (**17g**)*: [Mp 53—54 °C, recrystallization from hexane (lit,[20] 50—52 °C)]: IR 3410 cm^{-1}; NMR δ=1.75 (m, 2H), 2.63—3.10 (m, 4H), 6.55—7.15 (m, 4H), 7.38—8.05 (br 1H).

*3-Isopropylindole (**17a-v**)*: To a solution of 3 mmol of LTMP in 4 mL of diglyme at −78 °C, 3 mL of hexamethylphosphoric triamide (HMPA) was added, and then 239 mg (1.5 mmol) of **17a-v** was dropwise added. After the mixture was stirred at −78 °C for 30 min, it was allowed to warm up to room temperature and quenched with aq NH_4Cl. 3-Isopropylindole (**17a-v**)[17] was isolated by preparative TLC [TLC(Silica gel, C_6H_6) R_f=0.85].

*3-Trimethylsilylindole (**17a-vii**)*: [Bp 104 °C (0.2 mmHg)] was prepared from **7a-vii** according to the procedure for the preparation of 3-methylindole (**17a-i**) except for that LDA was used in place of LTMP. IR 3410, 1252, 847 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=−0.04 (s, 9H), 6.37 (m, 1H), 6.8—7.2 (m, 3H), 7.3—7.7 (m, 2H). Found: C, 69.54; H, 7.76; N, 7.18%. Calcd for $C_{11}H_{15}NSi$: C, 69.78; H, 7.99; N, 7.40%.

*3-(Methylthio)indole (**17a-viii**)*: [Bp 120 °C (0.1 mmHg)] [lit,[6d] bp 112—113 °C (0.15 mmHg)] was prepared from **7a-viii** according to the procedure for the preparation of **17a-vii**.

*2-Ethyl-4-methylphenyl Isocyanide (**7b-i**). General Procedure for Selective Alkylations at the ortho-Methyl Group of 2,4-Dimethylphenyl Isocyanide (**1b**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added 197 mg of 2,4-dimethylphenyl isocyanide (**1b**). After 30 min, 426 mg (3 mmol) of methyl iodide was added to the mixture at −78 °C. The reaction mixture was worked up in the usual way and distilled to afford 2-ethyl-4-methylphenyl isocyanide (**7b-i**) [bp 70 °C (1 mmHg)] in 93% yield. IR 2125 cm^{-1}; NMR(CCl_4 with Me_4Si) δ=1.26 (t, 3H), 2.32 (s, 3H), 2.69 (q, 2H), 6.8—7.2 (m, 3H). Found: C, 82.66; H, 7.85; N, 9.88%. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65%.

2-Alkyl-4-methylphenyl Isocyanide (**7b-ii**) and (**7b-iii**) were prepared according to the above procedure.

*2-Pentyl-4-methylphenyl Isocyanide (**7b-ii**)*: [Bp 80 °C (1 mmHg)]: IR 2120 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.88 (t, 3H), 1.2—1.6 (m, 6H), 2.30 (s, 3H), 2.63 (t, 2H), 6.8—7.2 (m, 3H). Found: C, 83.51; H, 9.29; N, 7.62%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

*2-(3-Butenyl)-4-methylphenyl Isocyanide (**7b-iii**)*: [Bp 54 °C (0.6 mmHg)]: IR 2115, 1638 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=2.37 (s, 3H), 2.44 (m, 2H), 2.88 (m, 2H), 4.8—5.2 (m, 2H), 5.5—6.1 (m, 1H), 6.8—7.2 (m, 3H). Found: C, 84.36; H, 7.89; N, 8.00%. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18%.

*2,4-Diethylphenyl Isocyanide (**12-i**). General Procedure for Selective Alkylations at the 4-Methyl Group of 2-Alkyl-4-methylphenyl Isocyanide (**7b**)*: To a solution of 3 mmol of LDA in 4 mL diglyme at −78 °C was added 218 m (1.5 mmol) of 2-ethyl-4-methylphenyl isocyanide (**7b-i**) and stirred for 30 min at the same temperature. To the red colored mixture, 426 mg (3 mmol) of methyl iodide was added. The usual work-up of the reaction mixture afforded 2,4-diethylphenyl isocyanide (**12-i**) [bp 57 °C (0.5 mmHg)] in 84% yield. IR 2120 cm^{-1}; NMR (CCl_4 with Me_4Si) δ= 1.20 (t, 3H), 1.28 (t, 3H), 2.56 (q, 2H), 2.68 (q, 2H), 6.8—7.2 (m, 3H). Found: C, 82.78; H, 8.43; N, 9.03%. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80%.

Similarly, 2,4-dialkylphenyl isocyanides (**12-ii**), (**12-iii**), and (**12-iv**) were prepared by alkylations of **7b**

*2,4-Dipentylphenyl Isocyanide (**12-ii**)*: [Bp 120 °C (0.4 mmHg)]: IR 2120 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.88 (t, 6H), 1.1—1.8 (m, 12H), 2.3—2.8 (m, 4H), 6.8—7.2 (m, 3H). Found: C, 83.69; H, 10.49; N, 5.95%. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76%.

*2-Pentyl-4-(3-butenyl)phenyl Isocyanide (**12-iii**)*: [Bp 116 °C (0.4 mmHg)]: IR 2120, 1640 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.92 (t, 3H), 1.2—1.6 (m, 6H), 2.1—2.8 (m, 6H), 4.7—5.0 (m, 2H), 5.3—5.8 (m, 1H), 6.7—7.2 (m, 3H). Found: C, 84.30; H, 9.08; N, 6.09%. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16%.

*2-(3-Butenyl)-4-isobutylphenyl Isocyanide (**12-iv**)*: [Bp 115 °C (0.6 mmHg)]: IR 2120, 1638 cm^{-1}; NMR(CCl_4 with M_4eSi) δ=0.93 (d 6H), 1.85 (m, 1H), 2.2—2.8 (m, 6H), 4.8—5.1 (m, 2H), 5.4—5.9 (m, 1H), 6.8—7.2 (m, 3H). Found: C, 84.75; H, 8.70; N, 6.34%. Calcd for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57%.

*2,4-Diethylphenyl Isocyanide (**12-i**). General Procedure for Direct Dialkylations of 2,4-Dimethylphenyl Isocyanide (**1b**)*: To a solution of 6 mmol of LDA in 8 mL of diglyme at −78 °C was added 197 mg (1.5 mmol) of 2,4-dimethylphenyl isocyanide (**1b**) and stirred for 30 min at the same temperature. To the red solution was added 852 mg (6 mmol) of methyl iodide and worked up in the usual way. 2,4-Diethylphenyl isocyanide (**12-i**) was obtained in 64% yield.

*3-Methyl-5-ethylindole (**18-i**). General Procedure for Preparations of 3,5-Dialkylindoles (**18**)*: To a solution of 3 mmol of LTMP in 4 mL of diglyme at −78 °C was added dropwise 239 mg (1.5 mmol) of 2,4-diethylphenyl isocyanide (**12-i**), and stirred for 30 min at the same temperature. The reaction mixture was allowed to warm up to room temperature and quenched with aq NH_4Cl. After the usual work-up, 3-methyl-5-ethylindole (**18-i**) was isolated in 39% yield by preparative TLC [TLC (Silica gel, $CHCl_3$) R_f=0.63]. IR 3400 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.27 (t, 3H), 2.25 (d,

3H), 2.69 (q, 2H), 6.62 (m, 1H), 6.85 (m, 2H), 7.16 (m, 1H), 7.8 (br 1H). Found: C, 83.01; H, 8.11; N, 8.99%. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80%.

2,4-Dialkylindoles (**18-ii**)—(**18-iv**) were prepared according to the above procedure.

*3-Butyl-5-pentylindole (**18-ii**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.84]: IR 3400 cm^{-1}; NMR δ=0.88 (t, 3H), 0.90 (t, 3H), 1.2—1.8 (m, 10H), 2.67 (t, 4H), 6.80 (m, 1H), 7.00 (m, 1H), 7.08 (m, 1H), 7.28 (m, 1H), 7.6 (br, 1H). Found: C, 83.78 H, 10.08; N, 5.49%. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76%.

*3-Butyl-5-(3-butenyl)indole (**18-iii**)*: [TLC (Silica gel, C_6H_6-hexane (1:1)) R_f=0.65] IR 3400, 1638 cm^{-1}; NMR δ=0.96 (t, 3H), 1.2—1.6 (m, 4H), 2.19 (m, 2H), 2.67 (m, 4H), 4.8—5.1 (m, 2H), 5.4—6.0 (m, 1H), 6.84 (m, 1H), 6.96 (m, 1H), 7.09 (m, 1H), 7.30 (m, 1H), 7.7 (br, 1H). Found: C, 84.82; H, 9.17; N, 6.00%. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16%.

*3-Allyl-5-isobutylindole (**18-iv**)*: [TLC (Silica gel, $CHCl_3$) R_f= 0.82]: IR 3400, 1636 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.85 (d, 6H), 1.85 (m, 1H), 2.45 (d, 2H), 3.34 (d, 2H), 4.8—5.1 (m, 2H), 5.6—6.1 (m, 1H), 6.54 (m, 1H), 6.79 (m, 2H), 7.09 (m, 1H), 7.3 (br, 1H). Found: C, 84.30; H, 8.72; N, 6.44%. Calcd for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57%.

*2-Methyl-6-pentylphenyl Isocyanide (**7d-i**). General Procedure for Monoalkylations of 2,6-Dimethylphenyl Isocyannide (**1d**)*: To a solution of 2.5 mmol[21] of LDA in 4 mL of diglyme at −78 °C was added dropwise 197 mg (1.5 mmol) of 2,6-dimethylphenyl isocyamide (**1d**) in 1 mL of diglyme and stirred for 30 min at the same temperature. 343 mg (2.5 mmol) of butyl bromide was added to the mixture, and then worked up in the usual way and distilled to give 2-methyl-6-pentylphenyl isocyanide (**7d-i**) [bp 95 °C (0.6 mmHg)] in 87% yield. IR 2110 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.93 (t, 3H), 1.2—1.6 (m, 6H), 2.38 (s, 3H), 2.64 (m, 2H), 6.94 (m, 3H). Found: C, 83.11; H, 8.95; N, 7.32%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

2-Methyl-6-isobutylphenyl isocyanide (**7d-ii**) was prepared according to the above procedure. **7d-ii** [bp 62 °C (0.4 mmHg)] : IR 2110 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.92 (d, 6H), 1.92 (m, 1H), 2.35 (s, 3H), 2.53 (d, 2H), 6.94 (m, 3H). Found: C, 83.09; H, 8.51; N, 7.85%. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09%.

*2,6-Dipentylphenyl Isocyanide (**13-i**). General Procedure for Selective Alkylation at the 2-Methyl Group of 2-Methyl-6-alkylphenyl Isocyanide (**7d**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C, 281 mg (1.5 mmol) of 2-methyl-6-pentylphenyl isocyanide (**7d-i**) was added dropwise, and stirred for 30 min at the same temperature. To the mixture, 411 mg (3 mmol) of butyl bromide was added then worked up in the usual way. 2,6-Dipentylphenyl isocyanide (**13-i**) [bp 112 °C (0.6 mmHg)] was distilled in 80% yield. IR 2110 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.92 (t, 6H), 1.2—1.7 (m, 12H), 2.63 (m, 4H), 6.94 (m, 3H). Found: C, 83.74; H, 10.01; N, 5.48%. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76%.

*2,6-Diethylphenyl Isocyanide (**13-ii**). General Procedure for Direct Dialkylations of 2,6-Dimethylphenyl Isocyanide (**1d**)*: To a solution of 6 mmol of LDA in 8 mL of diglyme at −78 °C was added 197 mg (1.5 mmol) of **1d** and stirred for 30 min at the same temperature. To the red colored solution of the dianion **6**, 852 mg (6 mmol) of methyl iodide was added, and worked up in the usual way. 2,6-Diethylphenyl isocyanide (**13-ii**) [bp 55 °C (0.4 mmHg)] was distilled in 75% yield. IR 2115 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.27 (t, 6H), 2.70 (q, 4H), 6.99 (m, 3H). Found: C, 82.81; H, 8.01; N, 8.57%. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80%.

2,6-Dipentylphenyl isocyanide (**13-i**) was prepared in 60% yield by the procedure for direct dialkylations.

*7-Pentylindole (**19-i**). General Procedure for Preparations of 7-Alkylindoles (**19**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added 281 mg (1.5 mmol) of 2-methyl-6-pentylphenyl isocyanide (**7d-i**) and stirred for 30 min at the same temperature. The mixture was allowed to warm up to room temperature, quenched with aq NH_4Cl, and worked up in the usual way. 7-Pentylindole [TLC (Silica gel, $CHCl_3$) R_f=0.59] was isolated in 66% yield by preparative TLC. IR 3410 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.85 (t, 3H), 1.1—1.7 (m, 6H), 2.52 (t, 2H), 6.25 (dd, 1H), 6.6—7.3 (m, 4H), 7.4 (br, 1H). Found: C, 83.55; H, 9.31; N, 7.35%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

7-Isobutylindole (**19-ii**)[22] was similarly prepared and isolated by preparative TLC [TLC (Silica gel, $CHCl_3$) R_f= 0.68]. IR 3410 cm; NMR δ=0.98 (d, 6H), 2.03 (m, 1H), 2.64 (d, 2H), 6.42 (dd, 1H), 6.7—7.1 (m, 3H), 7.40 (m, 1H), 7.9 (br, 1H).

*3-Methyl-7-ethylindole (**20-ii**). General Procedure for Preparations of 3,7-Dialkylindoles (**20**)*: To a solution of 3 mmol of LTMP in 4 mL of digylme at −78 °C was added 239 mg (1.5 mmol) of 2,6-diethylphenyl isocyanide (**13-ii**) and stirred for 30 min at the same temperature. The purple solution was allowed to warm up to room temperature, and stirred for 30 min at room temperature. After the mixture was quenched with aq NH_4Cl, it was worked up in the usual way. 3-Methyl-7-ethylindole [bp 90 °C (0.6 mmHg)] was distilled in 63% yield. IR 3400 cm^{-1}; NMR δ=1.31 (t, 3H), 2.32 (d, 3H), 2.68 (q, 2H), 6.39 (q, 1H), 6.7—7.4 (m, 3H), 7.5 (br, 1H). Found: C, 82.77; H, 8.05; N, 8.95%. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80%.

3-Butyl-7-pentylindole (**20-i**) was similarly prepared and isolated by preparative TLC [TLC (Silica gel, C_6H_6) R_f= 0.79]: IR 3400 cm^{-1}; NMR δ=0.91 (t, 3H), 0.96 (t, 3H), 1.2—1.7 (m, 10H), 2.76 (m, 4H), 6.50 (m, 1H), 6.8—7.5 (m, 3H), 7.6 (br, 1H). Found: C, 83.59; H, 10.30; N, 5.49%. Calcd for $C_{17}H_{25}N$: C, 83.89 ; H, 10.35; N, 5.76%.

*α-Ethylindole-7-ethanol (**19-iii**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C, 197 mg (1.5 mmol) of 2,6-dimethylphenyl isocyanide (**1d**) was added and stirred at the same temperature for 30 min. To the red solution, 174 mg (3 mmol) of propionaldehyde was added at −78 °C. The red color of **2d** turned light yellow soon. Next, a solution of 3 mmol of LDA in 4 mL at −78 °C was added to the light yellow solution, and stirred for 30 min at −78 °C. The reaction mixture, which became red again, was allowed to warm up to room temperature and quenched with aq NH_4Cl. The usual work-up afforded α-ethylindole-7-ethanol in 57% yield [TLC (Silica gel, $CHCl_3$-AcOEt (1:4)) R_f= 0.36]: IR 3400, 3300 cm^{-1}; NMR (CCl_4 with Me_4Si) δ= 0.94 (t, 3H), 1.39 (m, 2H), 2.5 (br, 1H), 2.77 (d, 2H), 3.54 (m, 1H), 6.25 (m, 1H), 6.6—6.9 (m, 3H), 7.20 (m, 1H), 9.1 (br, 1H). Found: C, 76.41; H, 8.18; N, 7.26%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40%.

*o-(1-Methylpentyl)phenyl Isocyanide (**22-i**). General Procedure for Alkylations of o-Alkylphenyl Isocyanide(**7a**)*: To a solution of 3 mmol of LTMP in 4 mL of diglyme at −78 °C, was added 197 mg (1.5 mmol) of *o*-ethylphenyl iso cyanide (**7a-i**), and stirred for 30 min at the same temperature. To the purple solution, 322 mg (3 mmol) of butyl bromide was added at −78 °C and worked up in the usual way. *o*-(1-Methylpentyl)phenyl isocyanide (**22-i**) [bp 68 °C (2 mmHg)] was isolated in 72% yield by distillation. IR 2115 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.88 (t, 3H), 1.1—1.8 (m, 9H), 2.5—3.3 (m, 1H), 6.9—7.4 (m, 4H). Found: C, 83.51; H, 9.00; N, 7.63%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

o-(1-Methylpentyl)phenyl isocyanide (**22-i**) was also pre-

pared by methylation of *o*-pentylphenyl isocyanide (**7a-iii**). *o*-Alkylphenyl isocyanides (**22-ii**) and (**22-iii**) were prepared according to the above procedure.

*o-Isopropylphenyl Isocyanide (**22-ii**)*: [Bp 50 °C (0.1 mmHg)]: IR 2120 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.32 (d, 6H), 3.1—3.5 (m, 1H), 7.19 (m, 4H). Found: C, 82.60; H, 7.44; N, 9.37%. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65%.

*o-(1-Methylthioethyl)phenyl Isocyanide (**22-iii**)*: [Bp 86 °C (1 mmHg)]: IR 2110 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.53 (d, 3H), 1.93 (s, 3H), 4.26 (q, 1H), 7.2—7.7 (m, 4H). Found: C, 67.93; H, 6.05; N, 7.71%. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90%.

*o-(1-Methylthioethyl)phenyl Isocyanide (**22-iii**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added 245 mg (1.5 mmol) of *o*-(methylthiomethyl)phenyl isocyanide (**7a-iii**), and stirred for 30 min at the same temperature. To the mixture, 426 mg (3 mmol) of methyl iodide was added at −78 °C and worked up in the usual way.

o-[Bis(methylthio)methyl]phenyl isocyanide (**22-iv**) and *o*-(1-trimethylsilylethyl)phenyl isocyanide (**22-v**) were prepared in the similar way.

*o-[Bis(methylthio)methyl]phenyl Isocyanide (**22-iv**)*: [Bp 90 °C (0.4 mmHg)]: IR 2115 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=2.08 (s, 6H), 5.00 (s, 1H), 7.1—7.5 (m, 4H). Found: C, 57.19; H, 5.12; N, 7.01%. Calcd for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69%.

*o-(1-Trimethylsilylethyl)phenyl Isocyanide (**22-v**)*: [Bp 52 °C (0.6 mmHg)]: IR 2130, 1250, 835 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=−0.06 (s, 9H), 1.30 (d, 3H), 2.71 (q, 1H), 6.7—7.2 (m, 4H). Found: C, 70.77; H, 8.40; N, 6.85%. Calcd for $C_{12}H_{17}NSi$: C, 70.87; H, 8.42; N, 6.89%.

*α-α-Dimethylindole-3-ethanol (**25a-i**). General Procedure for One Pot Syntheses of Tryptophol Derivatrives (**25**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added 176 mg (1.5 mmol) of *o*-tolyl isocyanide (**1a**) and stirred for 30 min at the same temperature. 216 mg (3 mmol) of 2,2-dimethyloxirane was added to the mixture at −78 °C and stirred. After 3 h, 3 mmol of LDA in 2 mL of diglyme was added to the mixture at −78 °C and stirred for additional 2 h. The resulting mixture was allowed to warm up to room temperature and worked up in the usual way. α,α-Dimethylindole-3-ethanol (**25a-i**) [bp 150 °C (0.5 mmHg); mp 92—93 °C (lit,[23] 93—94 °C)] was produced in 68% yield. IR 3400, 3300 cm^{-1}; NMR δ=1.24 (s, 6H), 1.51 (s, 1H), 2.80 (s, 2H), 6.8—7.6 (m, 5H), 8.20 (br, 1H). Tryptophol derivatives (**25a-ii**)[24]—(**25e-viii**) were prepared according to the above procedure.

*α-Methylindole-3-ethanol (**25a-iii**)*: [Bp 155 °C (0.5 mmHg) (lit,[23] 140—145 °C (0.05 mmHg)); mp 129—133 °C]: IR 3400, 3300 cm^{-1}; NMR δ=1.26 (d, 3H), 2.2 (br, 1H), 2.85 (m, 2H), 4.03 (m, 1H), 7.0—7.7 (m, 5H), 8.0 (br, 1H).

*2-(3-Indolyl)cyclohexanol (**25a-iv**)*:[25] [Bp 170 °C (0.1 mmHg); mp 168 °C]: IR 3450, 3220 cm^{-1}; NMR δ=1.0—2.0 (m, 9H), 2.5 (m, 1H), 3.8 (m, 1H), 6.9—7.7 (m, 5H), 8.1 (br, 1H). The reaction of *o*-(lithiomethyl)phenyl isocyanide (**2a**) and cyclohexene oxide was slow and took 5 h at −78 °C before the second addition of LDA.

*α,α,5-Trimethylindole-3-ethanol (**25b-v**)* (48% yield) was produced together with 2,4-bis(3-hydroxy-3-methylbutyl)-phenyl isocyanide (**26b-v**) (15% yield), which were separated and isolated by preparative TLC. **25b-v** [TLC (Silica gel, $CHCl_3$-AcOEt (5:2)) R_f=0.46]: IR 3400, 3300 cm^{-1}; NMR δ=1.09 (s, 6H), 1.79 (br s, 1H), 2.32 (s, 3H), 2.65 (s, 2H), 6.57 (m, 1H), 6.80 (m, 2H), 7.17 (m, 1H), 8.2 (br, 1H). Found: C, 76.56; H, 8.20; N, 6.65%. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%. **26b-v** [TLC (Silica gel, $CHCl_3$-AcOEt (5:2)) R_f=0.12]: IR 3350, 2121 cm^{-1}; NMR δ=1.17 (br s, 12H), 1.70 (m, 4H), 2.32 (br, 2H), 2.72 (m, 4H), 6.8—7.2 (m, 3H). Found: C, 73.96; H, 9.22; N, 5.28%. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09%.

α,5-Dimethylindole-3-ethanol (**25b-vi**) (48% yield) was produced with 2,4-bis(3-hydroxybutyl)phenyl isocyanide (**26b-vi**) (17% yield). **25b-vi** [Bp 160 °C (0.5 mmHg)]: IR 3400, 3300 cm^{-1}; NMR δ=1.25 (d, 3H), 1.85 (br s, 1H), 2.39 (s, 3H), 2.78 (m, 2H), 4.03 (m, 1H), 6.93 (d, 1H), 7.0—7.4 (m, 3H), 8.1 (br, 1H). Found: C, 75.94; H, 8.08; N, 7.57%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40%. **26b-vi** [TLC (Silica gel, $CHCl_3$-AcOEt (5:2)) R_f=0.14]: IR 3350, 2120 cm^{-1}; NMR δ=1.18 (d, 3H), 1.21 (d, 3H), 1.77 (m, 4H), 2.4—2.9 (m, 6H), 3.6—4.0 (m, 2H), 6.8—7.2 (m, 3H). Found: C, 72.63; H, 8.34; N, 5.88%. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66%.

α,α,7-Trimethylindole-3-ethanol (**25d-vii**) (23% yield) was produced with 7-(3-hydroxy-3-methylbutyl)indole (**27d-vii**) (33% yield). **25d-ii** [TLC (Silica gel, $CHCl_3$-AcOEt (4:1)) R_f=0.49]: IR 3400, 3350 cm^{-1}; NMR δ=1.23 (s, 6H), 1.82 (s, 1H), 2.38 (s, 3H), 2.80 (s, 2H), 6.90 (m, 3H), 7.35 (m, 1H), 8.1 (br, 1H). Found: C, 76.55; H, 8.22; N, 6.51%. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%. **27d-vii** [TLC (Silica gel, $CHCl_3$-AcOEt (4:1)) R_f=0.18]: IR 3400, 3300 cm^{-1}; NMR δ=1.27 (s, 6H), 1.94 (m, 2H), 2.42 (br s, 1H), 2.80 (m, 2H), 6.7—7.4 (m, 5H), 9.4 (br, 1H). Found: C, 76.64; H, 8.18; N, 6.66%. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%.

*1-Methylindole (**30a-i**). General Procedure for Preparations of 1-Substitued Indoles (**30**)*: To a solution of 3 mmol of LDA in 4 mL of diglyme at −78 °C was added 176 mg (1.5 mmol) of **1a**, and stirred for 30 min at the same temperature. After the reaction mixture was allowed to warm up to room temperature, 426 mg (3 mmol) of methyl iodide was added dropwise to the resulting light yellow solution, and stirred for 1 h at room temperature. The progress of the alkylation can be monitored by TLC or GLC. The mixture was worked up in the usual way to give 1-methylindole (**30a-i**) [bp 85 °C (1 mmHg) (lit,[26] 103—105 °C (2 mmHg))] in 82% yield. NMR δ=3.69 (s, 3H), 6.42 (d, 1H) 6.9—7.3 (m, 4H), 7.5—7.7 (m, 1H).

1-Substituted indoles (**30a-ii**)—(**30a-x**) were prepared according to the above procedure.

*1-Butylindole (**30-ii**)*:[27] [Bp 114 °C (2 mmHg)]: NMR δ=0.93 (t, 3H), 1.0—2.0 (m, 4H), 4.02 (t, 2H), 6.31 (d, 1H), 6.8—7.2 (m, 4H), 7.4—7.6 (m, 1H).

*1-(Methoxycarbonylmethyl)indole (**30a-iii**)*:[28] [Bp 119 °C (2 mmHg)]: IR 1733 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=3.56 (s, 3H), 4.66 (s, 2H), 6.32 (d, 1H), 6.82 (d, 1H), 6.9—7.1 (m, 2H), 7.3—7.5 (m, 1H).

*1-(Trimethylsilyl)indole (**30a-iv**)*: [Bp 74 °C (0.4 mmHg) (lit,[29] 82—84 °C (0.4 mmHg))].

*1-Propionylindole (**30a-v**)*: [Bp 93 °C (1 mmHg); mp 59—60 °C (lit,[30] 60.5—61 °C)]: IR 1697 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=1.21 (t, 3H), 2.74 (q, 2H), 6.40 (d, 1H), 6.9—7.4 (m, 4H), 8.2—8.4 (m, 1H).

*1-(Methoxycarbonyl)indole (**30a-vi**)*:[31] [Bp 100 °C (2 mmHg)]: IR 1736 cm^{-1}; NMR δ=3.96 (s, 3H), 6.55 (d, 1H), 7.1—7.6 (m, 4H), 8.0—8.2 (m, 1H).

*α-Ethylindole-1-ethanol (**30a-vii**)*: [Bp 125 °C (1 mmHg)]: IR 3350 cm^{-1}; NMR δ=1.02 (t, 3H), 1.2—1.7 (m, 2H), 2.0 (br, 1H), 3.8—4.2 (m, 3H), 6.56 (d, 1H), 7.1—7.8 (m, 5H). Found: C, 75.95; H, 7.84; N, 7.15%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40%.

*α-Methylindole-1-ethanol (**30a-viii**)*: [Bp 117 °C (1 mmHg)]: IR 3350 cm^{-1}; NMR δ=1.08 (d, 3H), 1.98 (s, 1H), 3.7—4.1 (m, 3H), 6.42 (d, 1H), 6.9—7.7 (m, 5H). Found: C, 75.19; H, 7.62; N, 7.77%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

*α,α-Dimethylindole-1-ethanol (**30a-ix**)*: [TLC (Silica gel,

$CHCl_3$-AcOEt (4:1)) R_f=0.76]: IR 3400 cm^{-1}; NMR δ= 1.24 (s, 6H), 1.42 (s, 1H), 4.00 (s, 2H), 6.43 (d, 1H), 6.9—7.6 (m, 5H). Found: C, 76.01; H, 7.72; N, 7.58%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40%.

*1-(2-Hydroxycyclohexyl)indole (**30a-x**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.49]: IR 3400 cm^{-1}; NMR δ=1.0—2.1 (m 9H), 3.2—4.1 (m, 2H), 6.32 (d, 1H), 6.9—7.6 (m, 5H). Found: C, 78.27; H, 8.12; N, 6.37%. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51%.

*1-Butyl-3-methylindole (**30a-xi**)*: To a solution of 3 mmol of LTMP in 4 mL of diglyme at −78 °C was added 197 mg (1.5 mmol) of *o*-ethylphenyl isocyanide (**7a-i**) and stirred for 30 min at the same temperature. After the mixture was allowed to warm up to room temperature, 322 mg (3 mmol) of butyl bromide was added dropwise and stirred for 1 h. The usual work-up of the reaction mixture afforded 1-butyl-3-methylindole (**30a-xi**)[31] [bp 170 °C (1 mmHg)] in 65% yield.

*o-(Acetylmethyl)phenyl Isocyanide (**31**). General Procedure for Acylations of **2** with N-Acylaziridines*: To a stirring solution of **2a** (7.5 mmol) in 20 mL of diglyme at −78 °C was added dropwise 1.28 g (15 mmol) of *N*-acetylaziridine. After the reaction mixture was stirred at the same temperature for 10 min, it was worked up in the usual way. *o*-(Acetylmethyl)phenyl isocyanide (**31-i**) (92%) was distilled at bp 105 °C (1 mmHg).[9]

o-[(4-Chlorobutyryl)methyl]phenyl isocyanide (**31-iii**) and *o*-[(4-hydroxybutyryl)methyl]phenyl isocyanide (**31-iv**) were prepared by the reaction of **2a** with ethyl 4-chlorobutyrate and γ-butyrolactone according to the procedure reported.[9]

31-iii [TLC (Silica gel, $CHCl_3$-AcOEt (100:1)) R_f=0.44]: IR 2110, 1718 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=2.15 (m, 2H), 2.80 (t, 2H), 3.61 (t, 2H), 3.91 (s, 2H), 7.0—7.8 (m, 4H). Found: C, 64.84; H, 5.59; N, 6.48%. Calcd for $C_{12}H_{12}NOCl$: C, 65.02; H, 5.46; N, 6.32%.

31-iv [TLC (Silica gel, $CHCl_3$-AcOEt (1:1)) R_f=0.43]: IR 3400, 2120, 1713 cm^{-1};NMR δ=1.83 (quintet, 2H), 2.2 (br, 1H), 2.67 (t, 2H), 3.59 (t, 2H), 3.87 (s, 2H), 7.27 (m, 4H). Found: C, 71.19; H, 6.70; N, 6.75%. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89%.

*o-(1-Acetylethyl)phenyl Isocyanide (**34-i**). General Procedure for Alkylations of o-(Acylmethyl)phenyl Isocyanide (**31**)*: To a stirring suspension of 48 mg (1 mmol, 50% in Oil) of NaH in 3 mL of DMSO-THF (1:1) at −20 °C was added 159 mg (1 mmol) of *o*-(acetylmethyl)phenyl isocyanide (**31-i**) in 1 mL of THF. After stirring for 15 min, the mixture was treated with 142 mg (1 mmol) of methyl iodide for 30 min. An extractive work-up gave 146 mg (84%) of *o*-(1-acetylethyl)phenyl isocyanide (**34-i**), bp 95 °C (0.4 mmHg). **34-i**: IR 2105, 1718 cm^{-1}; NMR δ=1.42 (d, 3H), 2.13 (s, 3H), 4.15 (q, 1H), 7.1—7.5 (m, 4H). Found: C, 76.44; H, 6.70; N, 8.22%. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09%.

*o-(1-Isovalerylethyl)phenyl Isocyanide (**34-ii**)*: [Bp 109 °C 0.2 mmHg)]: IR 2105, 1722 cm^{-1}; NMR δ=0.85 (d, 6H), 1.35 (d, 3H), 2.00—2.45 (m, 3H), 4.05 (q, 1H), 7.0—7.4 (m, 4H). Found: C, 78.03; H, 8.12; N, 6.68%. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51%.

*o-(1-Pivaloylethyl)phenyl Isocyanide (**34-iii**)*: [Bp 120 °C (0.6 mmHg)]: IR 2105, 1710 cm^{-1}; NMR δ=1.05 (s, 9H), 1.44 (d, 3H), 4.57 (q, 1H), 7.1—7.5 (m, 4H). Found: C, 77.91; H, 8.15; N, 6.68%. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51%.

*o-(1-Pivaloyl-2-methylpropyl)phenyl Isocyanide (**34-iv**)*: [Bp 105 °C (0.3 mmHg)]: IR 2105, 1703 cm^{-1}; NMR (CCl_4 with Me_4Si) δ=0.91 (d, 6H), 1.00 (s, 9H), 2.0—2.5 (m, 1H), 4.11 (d, 1H), 7.0—7.5 (m, 4H). Found: C, 79.03; H, 8.98; N, 5.54%. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76%.

*o-(1-Pivaloyl-3-oxobutyl)phenyl Isocyanide (**34-v**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.62]: IR 2105, 1720, 1705 cm^{-1}; NMR δ= 1.13 (s, 9H), 2.15 (s, 3H), 2.56 (dd, 1H), 3.36 (dd, 1H), 5.03 (dd, 1H), 7.1—7.5 (m, 4H). Found: C, 74.44; H, 7.30; N, 5.66%. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%.

*2-(1-Pivaloyl-2-cyanoethyl)phenyl Isocyanide (**34-vi**)*: [TLC (Silica gel, $CHCl_3$-AcOEt (40:1)) R_f=0.47]: IR 2238, 2115, 1700 cm^{-1}; NMR δ=1.09 (s, 9H), 2.56 (dd, 2H), 4.94 (t, 1H), 7.2—7.7 (m, 4H). Found: C, 74.81; H, 6.52; N, 11.85%. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66%.

*o-(1-Benzoyl-3-butenyl)phenyl Isocyanide (**34-vii**)*: [TLC (Silica gel, hexane-C_6H_6 (1:1)) R_f=0.80]: IR 2110, 1725, 1645 cm^{-1};NMR δ=2.4—2.9 (m, 2H), 4.6—5.5 (m, 3H), 5.5—6.4 (m, 1H), 7.1—7.6 (m, 6H), 7.8—8.1 (m, 3H). Found: C, 82.89; H, 5.55; N, 5.58%. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36%.

*2-[1-Pivaloyl-2-(ethoxycarbonyl)ethyl]-4-methylphenyl Isocyanide (**34-viii**)*: [TLC (Silica gel, $CHCl_3$-AcOEt (10:1)) R_f=0.54]: IR 2110, 1730, 1715 cm^{-1}; NMR δ=1.10 (s, 9H), 1.28 (t, 3H), 2.26 (s, 3H), 2.43 (dd, 1H), 3.02 (dd, 1H), 4.03 (q, 2H), 4.90 (dd, 1H), 6.8—7.9 (m, 3H). Found: C, 71.63; H, 7.88; N, 4.50%. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65%.

*2-(1-Pivaloyl-3-butenyl)-6-methylphenyl Isocyanide (**34-ix**)*: [Bp 130 °C (0.4 mmHg)]: IR 2105, 1709, 1640 cm^{-1}; NMR δ=1.06 (s, 9H), 2.45 (s, 3H), 2.4—3.0 (m, 2H), 4.5—5.2 (m, 3H), 5.4—6.0 (m, 1H), 7.1—7.6 (m, 3H). Found: C, 80.09; H, 8.38; N, 5.72%. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%.

*2,3-Dimethylindole (**35-i**). General Procedure for Preparations of 2,3-Disubstituted Indole (**35**)*: A mixture of 173 mg (1 mmol) of *o*-(1-acetylethyl)phenyl isocyanide (**34-i**) and 6 mL of *ca.* 6% HCl in 5:1 methanol-water was stirred for 30 min at room temperature. Then, the mixture was made alkaline by adding 10% aqueous NaOH and stirred for 30 min. An extractive work-up, followed by recrystallization from hexane afforded 90 mg (62%) of 2,3-dimethylindole (**35-i**), mp 106—107 °C (lit,[15b] 105—107 °C).

*2-Isobutyl-3-methylindole (**35-ii**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.85]: IR 3400 cm^{-1}; NMR δ=0.99 (d, 6H), 2.20 (s, 3H), 2.54 (d, 2H), 1.95—2.62 (m, 1H), 7.1—8.1 (m, 5H). Found: C, 83.38; H, 9.30; N, 7.61%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

*2-t-Butyl-3-methylindole (**35-iii**)*:[32] [TLC (Silica gel, hexane-C_6H_6 (1:1)) R_f=0.60]: IR 3420 cm^{-1}: NMR δ= 1.40 (s, 9H), 2.31 (s, 3H), 6.8—7.5 (m, 4H), 7.5—7.9 (br, 1H). Found: C, 83.52; H, 9.01; N, 7.30%. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48%.

*2-t-Butyl-3-isopropylindole (**35-iv**)*: [TLC (Silica gel, hexane-C_6H_6 (1:1)) R_f=0.74] (mp 100—102.5 °C): IR (KBr disk) 3430 cm^{-1}; NMR δ=1.42 (s, 9H), 1.45 (d, 6H), 3.44 (m, 1H), 6.8—7.3 (m, 3H), 7.5—7.8 (m, 2H). Found: C, 83.83; H, 10.02; N, 6.73%. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51%.

*2-t-Butyl-3-(2-oxopropyl)indole (**35-v**)*: [TLC (Silica gel, $CHCl_3$-AcOEt (10:1)) R_f=0.57]: IR 3380, 1697 cm^{-1}; NMR δ=1.40 (s, 9H), 2.05 (s, 3H), 3.84 (s, 2H), 6.9—7.5 (m, 4H), 8.1—8.5 (br, 1H). Found: C, 78.72; H, 8.18; N, 5.96%. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11%.

*2-t-Butyl-3-(cyanomethyl)indole (**35-vi**)*: [TLC (Silica gel, $CHCl_3$-AcOEt (40:1)) R_f=0.53]: IR 3375, 2235 cm^{-1}: NMR δ=1.41 (s, 9H), 3.90 (s, 2H), 7.0—7.6 (m, 4H), 7.8—8.5 (br, 1H). Found: C, 79.50; H, 7.81; N, 13.32%. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20%.

*2-Phenyl-3-allylindole (**35-vii**)*: [TLC (Silica gel, hexane-C_6H_6 (1:1)) R_f=0.53]: IR 3390, 1635 cm^{-1}; NMR δ=3.5—3.8 (m, 2H), 4.8—5.3 (m, 2H), 5.8—6.5 (m, 1H), 6.9—8.8

(m, 10H). Found: C, 87.35; H, 6.71; N, 5.98%. Calcd for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00%.

*2-t-Butyl-3-(ethoxycarbonylmethyl)-5-methylindole (**35-viii**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.22]: IR 3390, 1725 cm^{-1}; NMR δ=1.29 (t, 3H),1.41 (s, 9H), 2.42 (s, 3H), 3.90 (s, 2H), 4.15 (q, 2H), 6.9—7.5 (m, 3H), 8.0 (br, 1H). Found: C, 74.85; H, 8.58; N, 5.01%. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%.

*2-t-Butyl-3-allyl-7-methylindole (**35-ix**)*: [TLC (Silica gel, hexane-C_6H_6 (1:1)) R_f=0.63]: IR 3470, 1638 cm^{-1}; NMR δ= 1.43 (s, 9H), 2.47 (s, 3H), 3.61 (m, 2H), 4.7—5.2 (m, 2H), 5.6—6.4 (m, 1H), 6.8—7.5 (m, 3H), 7.7 (br 1H). Found: C, 84.28; H, 9.11; N, 6.01%. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16%.

*2-(3-Chloropropyl)indole (**33-i**)*: [TLC (Silica gel, $CHCl_3$) R_f=0.64]: IR 3375 cm^{-1}; NMR δ=2.11 (quintet, 2H), 2.88 (t, 2H), 3.58 (t, 2H), 6.30 (m, 1H), 7.1—7.7 (m, 4H), 7.8 (br, 1H). Found: C, 68.44; H, 6.40; N, 7.29%. Calcd for $C_{11}H_{12}NCl$: C, 68.22; H, 6.25; N, 7.23%.

*2-(3-Hydroxypropyl)indole (**33-ii**)*: [TLC (Silica gel. $CHCl_3$-AcOEt (10:1)] R_f=0.24] (mp 53—55 °C): IR (KBr disk) 3390, 3300 cm^{-1}; NMR δ=1.6—2.1 (m, 3H), 2.65 (t, 2H), 3.54 (t, 2H), 6.14 (m, 1H), 6.9—7.6 (m, 4H), 8.2 (br, 1H). Found: C, 75.59; H, 7.31; N, 8.10%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

References

1) U. Schöllkopf and F. Gerhart, *Angew. Chem.*, **80**, 842 (1968).

2) D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, **13**, 789 (1974); U. Schöllkopf, *ibid.*, **16**, 339 (1977).

3) T. Saegusa and Y. Ito, "Isonitrile Chemistry," Academic Press, New York, N. Y. (1971), pp. 65—92, and references cited therein.

4) H. M. Walborsky and G. E. Niznik, *J. Am. Chem. Soc.*, **91**, 7778 (1969).

5) Y. Ito, K. Kobayashi, and T. Saegusa, *J. Am. Chem. Soc.*, **99**, 3532 (1977).

6) a) E. Fischer and F. Jourden, *Chem. Ber.*, **16**, 2241 (1883); b) E. Fischer, *Justis Liebigs Ann. Chem.*, **236**, 126 (1886); c) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y. (1970); d) P. G. Gassmann, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); e) J. Bakke, H. Heikman, and E. B. Hellgran, *Acta Chem. Scand., Ser. B*, **28**, 134 (1974); f) L. S. Hegedus, G. S. Allen, and E. L. Watermann, *J. Am. Chem. Soc.*, **98**, 2673 (1976); g) M. Mori and Y. Ban, *Tetrahedron Lett.*, **1976**, 1803; h) R. R. Bard and J. F. Bunnett, *J. Org. Chem.*, **45**, 1546 (1980).

7) *o*-(Lithiomethyl)phenyl isocyanides (**2**) reacted at −78 °C with ketones and aldehydes to give *o*-(2-hydroxyalkyl)phenyl isocyanides in excellent yields. Attempts to cyclize *o*-(2-hydroxyalkyl)phenyl isocyanides *via* the ortho-benzylic lithiation afforded indole-3-methaol derivatives in low yields. Y. Ito, K. Kobayashi, and T. Saegusa, *Tetrahedron Lett.*, **1978**, 2087.

8) *o*-(Lithiomethyl)phenyl isocyanides (**2**) reacted with α,β-unsaturated esters in a conjugate addition to furnish 4-(*o*-isocyanophenyl)butyrates in good yields, which were converted on the ortho-benzylic lithiation to indole-3-propionates in low yields. Y. Ito, K. Kobayashi, M. Maeno, and T. Saegusa, *Chem. Lett.*, **1980**, 487.

9) Y. Ito, K. Kobayashi, and T. Saegusa, *J. Org. Chem.*, **44**, 2030 (1979).

10) The addition of *o*-(s-alkyl)phenyl isocyanides (**22**) to 2 equiv of LTMP in diglyme at −78 °C gave rise to a purple solution, suggesting the formtion of the expected benzylic carbanions. No cyclization product was obtained on warming up the purple solution. Unexpectedly, *o*-(1-methylthioethyl)phenyl isocyanide (**22-iii**) was treated with LTMP at −78 °C followed by warming up to room temperature to give 3-methylindole in good yield.

11) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

12) I. Ugi and R. Meyer, *Org. Synth.*, Coll. Vol. V, 1060 (1973).

13) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y. (1969), Vol. 2, p. 10.

14) O. M. H. El Dusouqui, M. Hassan, A. R. H. El Nad, and G. Yousif, *J. Chem. Soc., Perkin Trans. 2*, **1976**, 359.

15) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," 2nd ed, Aldrich Chemical Co., Milwaukee, Wis. (1975), and C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra," Aldrich Chemical Co., Milwaukee, Wis. (1974). a) Vol. 2, 1079A and Vol. 8, 51A. b) Vol. 2, 1079E and Vol. 8, 51D. c) Vol. 2, 1082A and Vol. 8, 55A. d) Vol. 2, 1081C and Vol. 8, 54B. e) Vol. 2, 1079B and Vol. 8, 51B.

16) R. R. Lorenz, B. F. Tullar, C. F. Kaelsch, and S. Arether, *J. Org. Chem.*, **30** 2531 (1965).

17) B. Cardillo, G, Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, **23**, 3771 (1967).

18) G. P. Buldrini, M. P. Panunzio, and A. Umani-Rocnch, *J. Chem. Soc., Chem. Commun.*, **1975**, 359.

19) J. Szmuszkovicz, *J. Org. Chem.*, **27**, 515 (1962).

20) A. B. A. Jansen, J. M. Johnson, and J. R. Sortees, *J. Chem. Soc.*, **1964**, 5573.

21) The use of 2 equiv of LDA resulted in the formation of a small amount of 2,6-dialkylphenyl isocyanides (**13**).

22) C. A. Demerson, L. G. Humber, and A. H. Philipp, *J. Med. Chem.*, **19**, 391 (1976).

23) M. Julia, H. Igolen, and J. Lenzi, *Bull. Soc. Chim. Fr.*, **1966**, 2291.

24) M. N. Preobrazhenskaya, K. K. Zhirnova, and N. P. Kostyuchenko, *Zh. Org. Khim.*, **8**, 994 (1972).

25) B. Heath-Brown and P. G. Philpott, *J. Chem Soc.*, **1965**, 7165.

26) N. Nakazaki and K. Yamamoto, *J. Org. Chem.*, **41**, 1877 (1976).

27) H. Plieninger, H. P. Kraemer, and C. Roth, *Chem. Ber.*, **108**, 1776 (1975).

28) S. Naruto, *Mem. Int. Sci. Ind. Res., Osaka Univ.*, **7**, 143 (1950).

29) R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, **38**, 3324 (1973).

30) A. G. Anastassiou, R. L. Eliott, and A. Lichtenfeld, *Tetrahedron Lett.*, **1972**, 4569.

31) N. E. Schore and N. J. Turro, *J. Am. Chem. Soc.*, **97**, 2488 (1975).

32) B. Robinson, *Chem. Ind.*, **1962**, 1291.