Synthesis of Indole Derivatives by Cu_2O-Catalyzed Cyclization of *o*-(*α*-Cyanoalkyl)phenyl Isocyanides and *o*-[*α*-(Methoxycarbonyl)alkyl]phenyl Isocyanides

Yoshihiko Ito, Yoshinori Inubushi, Toru Sugaya, Kazuhiro Kobayashi, and Takeo Saegusa

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606

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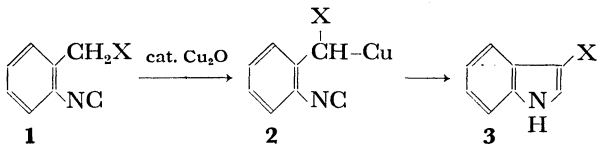
o-(Cyanomethyl)phenyl isocyanide and *o*-(methoxycarbonylmethyl)phenyl isocyanide were heated with a catalytic amount of Cu_2O in benzene to give 3-cyanoindole and 3-(methoxycarbonyl)indole in 86 and 92% yields, respectively. Lithiations of *o*-(cyanomethyl)phenyl isocyanide and *o*-(methoxycarbonylmethyl)phenyl isocyanide with butyllithium at −78 °C followed by the reaction with alkyl halides such as methyl iodide, allyl bromide, butyl bromide, benzyl bromide and methyl α-bromoacetate afforded the corresponding *o*-(α-cyanoalkyl)phenyl isocyanides and *o*-[α-(methoxycarbonyl)alkyl]phenyl isocyanides. *o*-(α-Cyanoalkyl)phenyl isocyanides and *o*-[α-(methoxycarbonyl)alkyl]phenyl isocyanides thus obtained were also cyclized by Cu_2O catalyst producing 3-alkyl-3-cyano-3*H*-indoles and 3-alkyl-3-(methoxycarbonyl)-3*H*-indoles, respectively, in moderate yields.

In the continuation of our studies[1] on synthetic reactions caused by Cu_2O-isonitrile complex, it has been found that the so-called active methylene compounds such as malonate, acetoacetate and cyclopentadiene were reacted with Cu_2O in the presence of isonitrile to produce organocopper(I) isonitrile complexes, which undergo an isonitrile insertion into their copper-carbon bonds.[2] On the basis of the isonitrile insertion of organocopper(I) isonitrile complexes, some heterocycle syntheses have been already reported.[3] Herein, we wish to report a new synthetic method of indole derivatives by the Cu_2O-catalyzed reactions of *o*-(cyanomethyl)phenyl isocyanide (**1a**) and *o*-(methoxycarbonylmethyl)phenyl isocyanide (**1b**),[4] in which intermediacy of the corresponding organocopper(I) isonitrile complexes (**2**) may by assumed.



1 **2** **3**

a: X=CN
b: X=CO_2CH_3

Results and Discussion

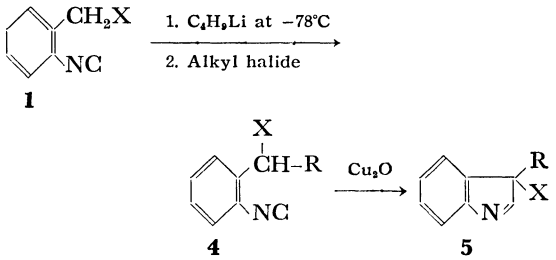
Isocyanides (**1a** and **1b**) were heated with a catalytic amount of Cu_2O to give 3-cyanoindole (**3a**)[5] and 3-(methoxycarbonyl)indole (**3b**)[6] in high yields, respectively. For example, a mixture of **1a** (2 mmol) and Cu_2O (0.025 mmol) in 2 ml of benzene was heated at 55 °C for 6 h with stirring. The progress of reaction was monitored by IR absorption band ($\nu_{N\equiv C}$=2150 cm^{-1}) characteristic of the starting isocyanide. After the insoluble copper catalyst was removed by filtration, the filtrate was evaporated and then subjected to column chromatography to give 3-cyanoindole (**3a**) in 86% yield.

o-(α-Cyanoalkyl)phenyl isocyanide (**4a**) and *o*-[α-(methoxycarbonyl)alkyl]phenyl isocyanide (**4b**), which were readily prepared *via* the lithiation of **1a** and **1b** followed by the reaction with alkyl halides (Table 1), were also cyclized by Cu_2O catalyst producing 3-alkyl-3-cyano-3*H*-indole (**5a**) and 3-alkyl-3-(methoxycarbonyl)-3*H*-indole (**5b**), respectively, in moderate yields. Results are summarized in Table 2.

Table 1. Alkylations of *o*-(cyanomethyl)phenyl isocyanide (**1a**) and *o*-(methoxycarbonylmethyl)phenyl isocyanide (**1b**)[a,b]

Starting phenyl isocyanide (**1**)	Alkyl halide	Product (**4**) (%)
1a	CH_3I	**4a-i** (76)
	i-C_3HBr	**4a-ii** (44)
	CH_2=$CHCH_2Br$	**4a-iii** (94)
	$C_6H_5CH_2Br$	**4a-iv** (83)
	$BrCH_2CO_2CH_3$	**4a-v** (57)
1b	CH_3I	**4b-i** (88)
	CH_2=$CHCH_2Br$	**4b-ii** (52)
	C_4H_9Br	**4b-iii** (51)

a) Alkylations of **1a** were performed by the lithiation of **1a** (5 mmol) with butyllithium (5 mmol) in 10 ml of THF at −78 °C followed by addition of alkyl halide (6 mmol). b) Alkylations of **1b** were performed by the lithiation of **1b** (1.5 mmol) with butyllithium (1.5 mmol) in 4 ml of diglyme and 1 ml of HMPA at −78 °C followed by addition of alkyl halide (2.0 mmol).



1 **4** **5**

a: X=CN
b: X=CO_2CH_3

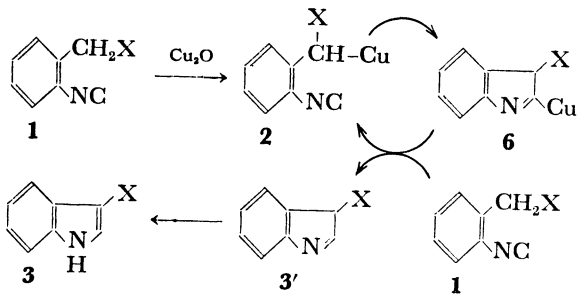
The following scheme involving organocopper(I) isonitrile complex (**2**) may be assumed for the present Cu_2O-catalyzed indole synthesis. The first step is the formation of **2**, in which an acidic hydrogen at the benzylic position of **1** is replaced by copper. The organocopper(I) isonitrile complex (**2**) subsequently undergoes an intramolecular isonitrile insertion to give a cyclic

Table 2. Indole synthesis by Cu_2O-catalyzed cyclizations of *o*-(α-cyanoalkyl)phenyl isocyanides and *o*-[α-(methoxycarbonyl)alkyl]-phenyl isocyanides

o-(α-Cyanoalkyl)-phenyl isocyanide and *o*-[α-(methoxycarbonyl)-alkyl]phenyl isocyanide	Reaction[a] Temp (°C)	Time (h)	Product (3) and (5) (%)
1a	55	6	**3a** (86)
1b	55	6	**3b** (92)
4a-i	70	10	**5a-i** (71)
4a-ii	80	18	**5a-ii** (61)
4a-iii	80	13	**5a-iii** (60)
4a-iv	80	25	**5a-iv** (62)
4a-v	80	6	**5a-v** (43)
4b-i	80	30	**5b-i** (80)
4b-ii	80	30	**5b-ii** (71)
4b-iii	80	30	**5b-iii** (88)

a) Cyclizations of **1** (and **4**) were performed by heating **1** (or **4**) (2 mmol) and Cu_2O (0.025 mmol) in 2 ml of benzene.

organocopper(I) intermediate (**6**). The abstraction of the acidic hydrogen of **1** by **6** produces indole derivative (**3**) regenerating **2** which initiates the next cycle of reaction.



Scheme 1.

The present indole synthesis is interestingly compared with the previously reported indole synthesis *via* the selective lithiation at the benzylic position of the alkyl group in *o*-alkylphenyl isocyanide and the subsequent cyclization.[4] The Cu_2O-catalyzed synthesis of indole is only applicable to *o*-alkylphenyl isocyanides which bear a benzylic hydrogen activated by cyano and ester groups. However, in view of the feasibility of the reaction conditions (a catalytic amount of Cu_2O and reaction temperature), the present method which complements our earlier procedure[4] is practically useful for the preparation of 3-cyano- and 3-(alkoxycarbonyl)indole derivatives.

Experimental

Materials. Cu_2O was commercially available and dried *in vacuo* prior to use. Alkyl halides and organic solvents all purified by distillation under nitrogen. *o*-(Cyanomethyl)phenyl isocyanide (mp 66 °C) (**1a**) was prepared in 78% yield according to the Ugi's procedure[7] from *o*-(formylamino)phenylacetonitrile which was prepared by formylation of *o*-aminophenylacetonitrile[8] with acetic formic anhydride.[9] *o*-(Methoxycarbonylmethyl)phenyl isocyanide (**1b**), bp 95 °C (0.6 Torr), was prepared in 69% yield by the reaction of *o*-(lithiomethyl)phenyl isocyanide with methyl chloroformate.[4]

*Cu_2O Catalyzed Cyclization of o-(Cyanomethyl)phenyl Isocyanide (**1a**).* A mixture of 284 mg (2 mmol) of *o*-(cyanomethyl)-phenyl isocyanide (**1a**), 3.6 mg (0.025 mmol) of Cu_2O and 2 ml of benzen was heated at 55 °C for 6 h with stirring under nitrogen. After the reaction mixture was filtered, the filtrate was distilled *in vacuo*. The residue was subjected to column chromatography (silica gel–chloroform) giving 3-cyanoindole (**3a**) in 86% yield. **3a** was identified by comparing the spectral data with those of the authentic sample.[5]

Cyclization reaction of *o*-(methoxycarbonylmethyl)phenyl isocyanide (**1b**) was carried out in a similar way. The product of 3-(methoxycarbonyl)indole (**3b**) (92% yield) was identified by comparing the spectral data with those of the authentic sample.[6]

*Reaction of o-(Cyanomethyl)phenyl Isocyanide (**1a**) with Methyl Iodide.* To a mixture of 710 mg (5 mmol) of *o*-cyanomethylphenyl isocyanide and 10 ml of THF cooled at −78 °C with stirring under nitrogen, butyllithium (5 mmol, 1.8 M hexane solution) was added. After 15 min, 0.37 ml (6 mmol) of methyl iodide was added dropwise to the mixture, which was then allowed to warm up to room temperature. The reaction mixture was filtered to remove insoluble inorganic salts and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with benzene–chloroform (5: 1) to yield *o*-(α-cyanoethyl phenyl)isocyanide (**4a-i**)(76% yield). Product of **4a-i** was identified by IR and NMR spectra.

Other alkylations of **1a** were carried out according to the procedure mentioned above.

*Reaction of o-(Methoxycarbonylmethyl)phenyl Isocyanide (**1b**) with Allyl Bromide.* To a mixture of 263 mg (1.5 mmol) of *o*-(methoxycarbonylmethyl)phenyl isocyanide (**1b**), 4 ml of diglyme and 1 ml of HMPA cooled at −78 °C, butyllithium (1.5 mmol, 1.8 M hexane solution) was added. After 15 min, 242 mg (2 mmol) of allyl bromide was added to the mixture and stirred for 1 h at −78 °C, which was then allowed to warm up to room temperature. The reaction mixture was poured into ether and washed with water, and dried over Na_2SO_4. The ether solution was evaporated *in vacuo* and subjected to column chromatography on silica gel eluting with chloroform to give 57% yield of *o*-[1-(methoxycarbonyl)-3-butenyl]phenyl isocyanide (**4b-ii**). Product of **4b-ii** was identified by IR and NMR spectra.

Other alkylations of **1b** were carried out according to the procedure mentioned above.

*General Procedure for Cu_2O Catalyzed Cyclization of o-(α-Cyanoalkyl)phenyl Isocyanide (**4a**) and o-[α-(Methoxycarbonyl)alkyl]phenyl Isocyanide (**4b**).* A mixture of 312 mg (2 mmol) of *o*-(α-cyanoethyl)phenyl isocyanide (**4a-i**), 3.6 mg (0.025 mmol) of Cu_2O and 2 ml of benzene was heated at 70 °C for 10 h with stirring under nitrogen. The reaction mixture was filtered, and the filtrate was subjected to vacuum distillation to afford 3-cyano-3-methyl-3*H*-indole (**5a-i**) in 71% yield, bp 95 °C (0.8 Torr). **5a-i**: IR (neat) 2225, 1605 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.68 (s, 3H), 7.3—7.8 (m, 4H), 7.98 (s, 1H). Found: C, 76.72; H, 5.20; N, 17.68%. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94%.

According to the above procedure, other *o*-(α-cyanoalkyl)-phenyl isocyanides (**4a**) and *o*-[α-(methoxycarbonyl)alkyl]-phenylisocyanides (**4b**) were cyclized.

*3-Cyano-3-isopropyl-3H-indole (**5a-ii**)*: Bp 105—108 °C (1 Torr), IR (neat) 2220, 1600 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.10 (d, 6H), 2.40 (m, 1H), 7.20—8.00 (m, 4H), 7.19 (s,

1H). Found: C, 78.41; H, 6.65; H, 15.03%. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21%.

*3-Cyano-3-allyl-3*H*-indole (**5a-iii**)*: Bp 110—112 °C (1 Torr), IR (neat) 2220, 1640, 1600 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 2.71 (d, 2H), 5.18 (m, 1H), 5.45 (m, 1H), 6.00 (m, 1H), 7.30—8.00 (m, 4H), 8.15 (s, 1H). Found: C, 79.32; H, 5.77; N, 15.45%. Calcd for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38%.

*3-Cyano-3-benzyl-3*H*-indole (**5a-iv**)*: was isolated by column chromatography on silica gel (benzene). **5a-iv**: IR (Neat) 2220, 1600 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 3.19 (s, 2H), 7.00—7.90 (m, 9H), 7.10 (s, 1H). Found: C, 82.93; H, 5.01; N, 12.28%. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06%.

*3-Cyano-3-(methoxycarbonylmethyl)-3*H*-indole (**5a—v**)*: was isolated by column chromatography on silica gel (chloroform). **5a—v**: IR (neat) 2210, 1740, 1600 cm^{-1}: NMR (CCl_4 with Me_4Si) δ 2.27 (s, 1H), 2.92 (s, 1H) 3.73 (s, 3H), 7.20—7.75 (m, 4H), 8.25 (s, 1H). Found: C, 67.51; H, 4.88; N, 12.91%. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08%.

*3-(Methoxycarbonyl)-3-methyl-3*H*-indole (**5b-i**)*: was isolated by column chromatography on silica gel (chloroform). **5b-i**: IR (neat) 1730. 1600 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.58 (s, 3H), 3.55 (s, 3H), 6.90—7.50 (m, 4H), 7.90 (s, 1H). Found: C, 69.58; H, 5.72; N, 7.28%. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%.

*3-(Methoxycarbonyl)-3-allyl-3*H*-indole (**5b-ii**)*: was isolated by column chromatography on silica gel (1:4 ethyl acetate–chloroform). **5b-ii**: IR (neat) 1730, 1640, 1600 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 2.70 (m, 2H), 3.64 (s, 3H), 5.0—5.6 (m, 3H), 6.80—7.50 (m, 4H), 7.95 (s, 1H). Found: C, 72.80; H, 6.11; N, 6.73%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%.

*3-(Methoxycarbonyl)-3-butyl-3*H*-indole (**5b-iii**)*: was isolated by column chromatography on silica gel (chloroform). **5b-iii**: IR (neat) 1730, 1590 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.83 (t, 3H), 1.20—1.50 (m, 4H), 2.00 (m, 2H), 3.68 (s, 3H). 7.00—7.60 (m, 4H), 8.18 (s, 1H). Found: C, 72.88; H, 7.59; N, 5.92%. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%.

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