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AN ONE-POT SYNTHESIS OF 3-ALKYLINDOLES FROM o-TOLYL ISOCYANIDES

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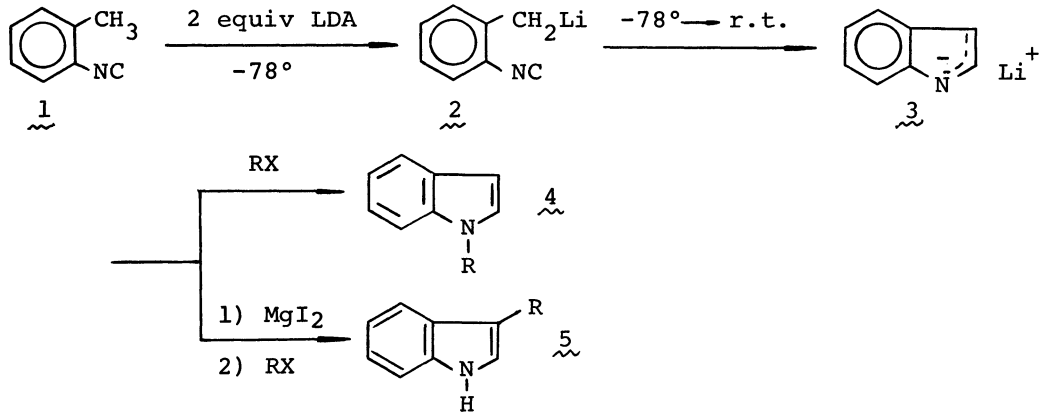
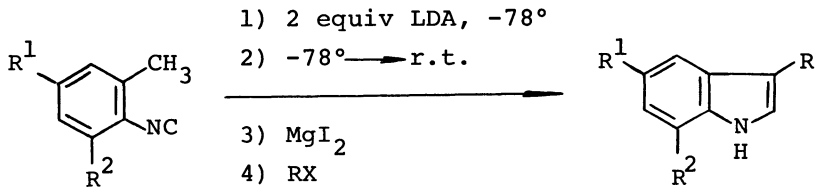
Indolyllithium arising from ring-closure of o-lithiomethylphenyl isocyanide, which is generated in situ by the reaction of o-tolyl isocyanide with lithium diisopropylamide in diglyme at -78°C, is treated with anhydrous MgI_2 prior to alkylations with alkyl halides to give 3-alkylindoles selectively in moderate to excellent yields. The reaction provides a convenient method for synthesis of 3-alkylindoles starting with o-tolyl isocyanide.

In the preceding papers,[1] it was described that o-tolyl isocyanide (1) was treated with lithium diisopropylamide (LDA) in diglyme at -78°C to generate o-lithiomethylphenyl isocyanide (2), which was conveniently utilized for the preparation of indoles and the related heterocycles.[2] As reported, the o-lithiomethylphenyl isocyanide (2) on warming up to room temperature was spontaneously cyclized to indolyllithium (3), which reacted with alkyl halides to afford N-alkyl indoles (4) in good yields.[1]



Now we found that the indolyllithium (3) thus generated was treated with anhydrous MgI_2 prior to alkylations to give 3-alkylindoles selectively in moderate to excellent yields. It is likely that the addition of MgI_2 has caused the conversion of 3 to indolylmagnesium iodide, since indolylmagnesium iodide is known to react with electrophiles to furnish 3-substituted indoles.[3] This reaction provides a convenient one-pot synthesis of 3-alkylindoles starting with o-tolyl isocyanide. A sample procedure is illustrated by the preparation of 3-benzylindole from o-tolyl isocyanide. A deep red solution of o-lithiomethyphenyl isocyanide (2) in diglyme prepared at -78° from 176 mg (1.5 mmol) of o-tolyl isocyanide and LDA (3.0 mmol) according to the reported procedure[1] was warmed up to

Table 1. One-pot Syntheses of 3-Alkylindoles



Run No	Isocyanide	RX	Yield (%)[a]	
1	1 (R^1=R^2=H)	$C_6H_5CH_2Br$	100	5a [b),c)]
2	1 (R^1=R^2=H)	CH_2=$CHCH_2Br$	80	5b [c), d)]
3	1 (R^1=R^2=H)	CH_3CH=$CHCH_2Cl$	85	5c
4	1 (R^1=R^2=H)	CH_2=$C(CH_3)CH_2Cl$	75	5d
5	1 (R^1=R^2=H)	CH_2=$C(Cl)CH_2Cl$	85	5e
6	1 (R^1=R^2=H)	CH_2=$C(COOCH_3)CH_2Cl$	88	5f [e)]
7	1 (R^1=R^2=H)	$HC{\equiv}CCH_2Br$	62	5g
8	1 (R^1=R^2=H)	n-C_4H_9Br	53	5h [b),e)]
9	1 (R^1=R^2=H)	iso-C_4H_9Br	47	5i [f)]
10	1 (R^1=R^2=H)	n-$C_8H_{17}Br$	69	5j
11	1 (R^1=R^2=H)	iso-C_3H_7I	20	5k [c)]
12	6 (R^1=CH_3, R^2=H)	CH_2=$CHCH_2Br$	87	8a
13	6 (R^1=CH_3, R^2=H)	n-C_4H_9Br	56	8b
14	7 (R^1=H, R^2=CH_3)	$C_6H_5CH_2Br$	43	9a [b)]
15	7 (R^1=H, R^2=CH_3)	CH_2=$CHCH_2Br$	70	9b [b)]
16	7 (R^1=H, R^2=CH_3)	n-$C_8H_{17}Br$	20	9c [b)]

a) Yields were determined by glc unless otherwise stated.
b) Isolated yields. c) Ref. 5a). d) Ref. 5b). e) Ref. 5c). f) Ref. 5d).

room temperature. To the resulting yellow-brown solution, 1.25 g (4.5 mmol) of anhydrous MgI_2,[4] which was prepared by reacting magnesium with an excess of methyl iodide in THF and then evaporating in vacuo, was added at once with stirring. After the mixture was stirred for 1 hr, 855 mg (5 mmol) of benzyl bromide was added dropwise at room temperature and stirred overnight. The reaction mixture was poured into aq NH_4Cl, extracted with ether and washed with brine. The ether extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel to afford 3-benzylindole (5a) in an almost quantitative yield (TLC on silica gel Rf=0.57 ($CHCl_3$ solvent)). Mp 111°C (lit.[5a] mp 110-111°C). 3a : IR (KBr disk) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 4.00 (s, 2H) 6.70 (s, 1H), 6.8-7.3 (m, 8H), 7.40 (m, 1H), 7.5-8.0 (broad 1H). Some one-pot syntheses of 3-substituted indoles were summarized in Table 1.[6]

As seen in the Table 1, the present method for the preparation of 3-substituted indoles starting with o-tolyl isocyanide is extended to 2,4-xylyl isocyanide (6) and 2,6-xylyl isocyanide (7). Following the above procedure, 2,4-xylyl isocyanide and 2,6-xylyl isocyanide were converted to 3-substituted-5-methylindoles (8) and 3-substituted -7-methylindoles (9), respectively, via selective lithiation at their ortho methyl groups followed by alkylations (Run No. 12~16).

Most syntheses of 3-alkylindoles, which have been hitherto known,[3] have been accomplished by alkylations of indole. The present synthetic method of 3-alkylindoles has an advantage over the previous methods in that indole skeleton is built up with introduction of alkyl substituent at the 3-position in one-flask starting with o-tolyl isocyanide commercially available.

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6. 5b : IR (neat) 3400, 1640 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 3.35 (s, 2H), 5.00 (m, 2H), 5.6-6.4 (m, 1H), 6.74 (m, 1H), 6.85-7.25 (m, 3H), 7.30-7.55 (m, 1H), 7.60-8.00 (broad, 1H).
   5c : IR (neat) 3400, 1620 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 1.58 (m, 3H), 3.22 (m, 2H), 5.35 (m, 2H), 6.45 (m, 1H), 6.80 -7.20 (m, 3H), 7.20-7.40 (m, 2H).
   5d : IR (neat) 3400, 1650 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.63 (s, 3H) 3.30 (s, 2H), 4.64 (m, 2H), 6.70 (m, 1H), 6.80-7.15 (m, 3H), 7.20-7.80 (m, 2H).

5e : IR (neat) 3400, 1632 cm^{-1}; NMR (DMSO-d_6 with Me_4Si) δ 3.70 (s, 2H), 5.10 (m, 2H), 6.78-7.75 (m, 5H), 9.33-9.95 (broad, 1H).

5f : TLC on silica gel, Rf=0.17 (1:1 C_6H_6-C_6H_{14}); IR (neat) 3400, 1705, 1630 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.25 (t, 3H), 3.65 (broads, 2H), 4.10 (q, 2H), 5.33 (m, 1H), 6.05 (m, 1H), 6.75-7.55 (m, 5H), 7.60-8.05 (broad, 1H).

5g : IR (neat) 3400, 3290, 2100 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 2.00 (t, 1H), 3.50 (dd, 2H), 6.66 (m, 1H), 6.95-7.18 (m, 3H), 7.25-7.88 (m, 2H).

5h : TLC on silica gel, Rf=0.63 (1:1 C_6H_6-C_6H_{14}); IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.88 (t, 3H), 1.03-1.97 (m, 4H), 2.65 (t, 2H), 6.73 (m, 1H), 6.78-7.20 (m, 3H), 7.30-7.50 (m, 2H).

5i : IR (neat) 3400 cm^{-1}; NMR (CCl_4 with Me_4Si) δ 0.96 (d, 6H), 1.96 (m, 1H), 2.61 (d, 2H), 6.86 (d, 1H), 7.00-7.30 (m, 3H), 7.40-7.70 (m, 1H), 7.70-8.00 (broad, 1H).

5j : IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.75 (t, 3H), 1.00-2.00 (m, 12H), 2.70 (t, 2H), 6.80-7.88 (m, 6H).

5k : IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.30 (d, 6H), 3.13 (sep, 1H), 6.63 (m, 1H), 6.70-7.23 (m, 3H), 7.23-7.88 (m, 2H).

8a : IR (neat) 3400, 1640 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 2.38 (s, 3H), 3.38 (d, 2H), 5.00 (m, 2H), 5.55-6.25 (m, 1H), 6.68 (m, 1H), 6.83-7.05 (m, 2H), 7.10-7.30 (m, 1H), 7.35-7.65 (broad, 1H).

8b : IR (neat) 3405 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.90 (t, 3H), 1.03-2.00 (m, 4H), 2.40 (s, 3H), 2.63 (t, 2H), 6.65 (m, 1H), 6.80-7.13 (m, 2H), 7.23 (d, 1H), 7.38-7.88 (broad, 1H).

9a : TLC on silica gel, Rf=0.50 (1:1 C_6H_6-C_6H_{14}); IR (KBr disk) 3410 cm^{-1}, NMR ($CDCl_3$ with Me_4Si) δ 2.33 (s, 3H), 3.95 (s, 2H), 6.63 (m, 1H), 6.75-7.35 (m, 8H), 7.38-7.80 (broad, 1H).

9b : TLC on silica gel, Rf=0.64 (1:1 C_6H_6-C_6H_{14}); IR (neat) 3410, 1640 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 2.33 (s, 3H), 3.38 (m, 2H), 5.00 (m, 2H), 5.55-6.25 (m, 1H), 6.63-7.38 (m, 4H), 7.40-7.80 (broad, 1H).

9c : TLC on silica gel, Rf=0.60 (1:1 C_6H_6-C_6H_{14}); IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.90 (t, 3H), 1.05-2.05 (m, 12H), 2.40 (s, 3H), 2.73 (t, 2H), 6.50-7.50 (m, 4H), 7.50-7.90 (broad, 1H).

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