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REACTIONS OF o-TOLYL ISOCYANIDE WITH ISOCYANATE AND ISOTHIOCYANATE ——— SYNTHESES OF N-SUBSTITUTED INDOLE-3-CARBOXAMIDES AND INDOLE-3-THIOCARBOXAMIDES

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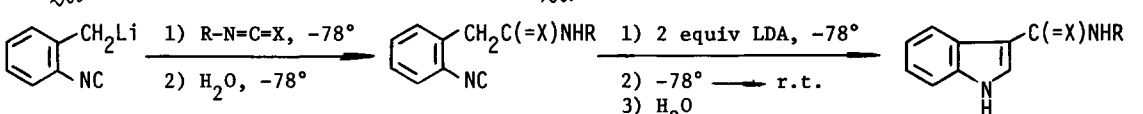
Summary: o-Lithomethylphenyl isocyanide is reacted at -78° with isocyanates and isothiocyanates to produce o-isocyanophenyl-acetamides (2a) and -acetothioamides (2b). Isocyanides 2a and 2b are cyclized to indole-3-carboxamides (3a) and -3-thiocarboxamides (3b) via lithiation, respectively. Isocyanides 2a are also cyclized by Cu_2O catalyst to produce 4,5-dihydro-1,3-benzodiazepin-4-ones (4a) with 3a.

In the preceding papers[1,2] we reported that o-lithiomethylphenyl isocyanide (1), which is generated in situ at -78° from o-tolyl isocyanide and lithium diisopropylamide (LDA), was a versatile intermediate for the preparation of indoles and the related compounds. In this paper we wish to report an elaboration of o-lithiomethylphenyl isocyanide (1) to N-substituted indole-3-carboxamides (3a) and indole-3-thiocarboxamides (3b), in which 1 was reacted with isocyanate and isothiocyanate, followed by cyclization of the resulting N-substituted o-isocyanophenylacetamides (2a) and o-isocyanophenylacetothioamides (2b).



1 2 3

a: X=O b: X=S

A sample procedure is illustrated by a synthesis of N-butyl indole-3-carboxamide. To a deep red solution of o-lithiomethylphenyl isocyanide in diglyme, which was prepared in situ at -78° by treating 176 mg (1.5 mmol) of o-tolyl isocyanide with LDA (3.0 mmol) in 4ml of diglyme according to the reported procedure,[1] was dropwise added 149 mg (1.5 mmol) of n-butyl isocyanate. The deep red color of 1 immediately turned to light red. After the reaction mixture was stirred for 30 min at -78°, it was quenched with aq NH_4Cl, extracted with ether, dried over anhydrous Na_2SO_4

and evaporated. The residue was distilled using Kugelrohr to afford N-butyl o-isocyanophenylacetamide (2a-i) in 70% yield (bp 125°/0.4 mmHg ; mp 95°), 2a-i : IR (neat) 3300, 2125, 1637 cm^{-1} ; NMR ($CDCl_3$ with TMS) δ 0.87 (t, 3H), 1.1~1.5 (m, 4H), 3.1 (m, 3H), 3.43 (s, 2H), 7.1~7.3 (m, 4H).

Next, 216 mg (1.0 mmol) of N-butyl o-isocyanophenylacetamide (2a-i) in 0.5 ml of diglyme was dropwise added to a solution of LDA (2 mmol) in 2.5 ml of diglyme at -78° with stirring. After the mixture was stirred for 30 min at -78° and then allowed to warm up to room temperature, it was poured into aq NH_4Cl and extracted with ether. The ether solution was concentrated in vacuo, and the residue was chromatographed on silica gel with 4:1 $CHCl_3$-AcOEt to give N-butyl indole-3-carboxamide (3a-i) (Tlc Rf=0.69) in 55% yield [mp 135° (lit[3] mp 131~131.5)] (Table 1).[4]

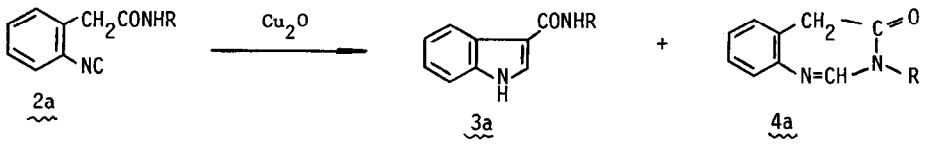
N-substituted indole-3-thiocarboxamides (3b) were prepared according to the same procedure except for that isothiocyanate was used in place of isocyanate. N-Substituted indole-3-thiocarboxamides can be also prepared in moderate yield in one-pot without isolating N-substituted o-isocyanophenylacetothioamides (2b) by successive addition of isothiocyanate and 2 equiv of LDA to o-lithiomethylphenyl isocyanide at -78°. However, the attempts to prepare N-substituted indole-3-carboxamides (3a) in one-pot were unsuccessful. Some syntheses of N-substituted indole-3-carboxamides (3a) and indole-3-thiocarboxamides (3b) were summarized in Table 2.[5]

Table 1. Preparations of N-Substituted o-Isocyanophenylacetamide (2a) and o-Isocyanophenylacetothioamides (2b)

R-N=C=X	Product (%)[a] 2a or 2b
$n\text{-}C_4H_9\text{-}N=C=O$	2a-i (70)
$c\text{-}C_6H_{11}\text{-}N=C=O$	2a-ii (55)
$tert\text{-}C_4H_9\text{-}N=C=O$	2a-iii (53)
$Ph\text{-}N=C=O$	2a-iv (50)
$c\text{-}C_6H_{11}\text{-}N=C=S$	2b-i (96)
$Ph\text{-}N=C=S$	2b-ii (82)

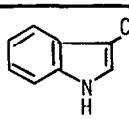
a) Isolated yields

N-Substituted o-isocyanophenylacetamides (2a) were also cyclized by Cu_2O catalyst to produce N-substituted indole-3-carboxamides (3a) and N-substituted 4,5-dihydro-1,3-benzodiazepin-4-ones (4a),[6] the ratio of 3a and 4a depending upon substituent on the amide nitrogen.



2a 3a 4a

Table 2. Preparations of N-Substituted Indole-3-carboxamides (3a) and Indole-3-thiocarboxamides (3b)

			Yield (%)[a]
R=n-C_4H_9,	X=O	(3a-i)	55
R=c-C_6H_{11},	X=O	(3a-ii)	60
R=tert-C_4H_9,	X=O	(3a-iii)	57
R=Ph,	X=O	(3a-iv)	68
R=c-C_6H_{11},	X=S	(3b-i)	60 (52)[b]
R=Ph,	X=S	(3b-ii)	58
R=CH_2=$CHCH_2$-,	X=S	(3b-iii)	— (58)[b]

a) Isolated yields from 2a or 2b

b) Overall yields from o-tolyl isocyanide (one-pot reaction)

Some results on the Cu_2O-induced cyclization of N-substituted o-isocyanophenylacetamides (Table 3) seem to indicate that the less bulky alkyl substituents on the amide nitrogen favor the formation of 4a.

The formations of 3a and 4a in the Cu_2O-induced cyclizations of 2a may be explained in terms of intramolecular isonitrile insertion[7,8] into the carbon-copper and the nitrogen-copper linkages of the organocopper intermediates 5 and 6, respectively, as shown in Scheme 1.

Scheme 1

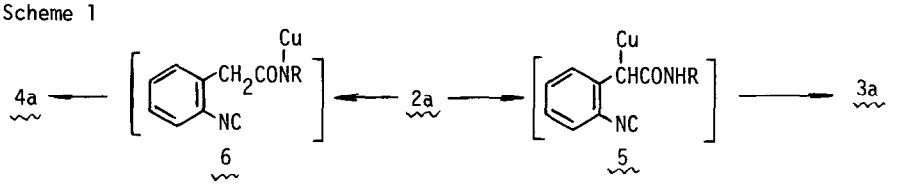
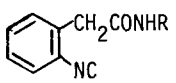


Table 3. Cu_2O Catalyzed Cyclizations of N-Substituted o-Isocyanophenylacetamides (2a)

		Reaction Time (hr)	Products (%)[a] 3a	4a
R=n-C_4H_9	(2a-i)	10[b]	0	85
R=c-C_6H_{11}	(2a-ii)	60[c]	25	58
R=tert-C_4H_9	(2a-iii)	60[c]	20[d]	0
R=Ph	(2a-iv)	10[b]	75	0

a) Isolated yields. b) 0.2 equiv of Cu_2O was used. c) 1 equiv of Cu_2O was used.

d) 60% of the starting amide (2a-iii) was recovered.

The Cu_2O induced cyclization of 2a was carried out as follows. A mixture of 242 mg (1 mmol) of N-cyclohexyl o-isocyanophenylacetamide (2a-ii), 143 mg (1 mmol) of Cu_2O and 10 ml of benzene was heated at reflux for 60 hr under nitrogen. The reaction mixture was filtered and the filtrate was distilled using Kugelrohr to afford N-cyclohexyl 4,5-dihydro-1,3-benzodiazepin-4-one (4a-ii) in 58% yield (bp 160°/0.6 mmHg ; mp 115°). The residue was chromatographed on silica gel with 1:1 $CHCl_3$-AcOEt to give N-cyclohexyl indole-3-carboxamide (3a-ii) (Tlc Rf=0.43) in 25% yield. 4a-ii : IR (KBr disk) 1666, 1622 cm^{-1}; NMR ($CDCl_3$ with TMS) δ 1.1~1.8 (m, 10H), 3.37 (s, 2H), 4.3 (m, 1H), 7.10 (m, 4H), 7.45 (s, 1H).

Cyclization of 2b with Cu_2O catalyst failed.

References and Notes

1. Y. Ito, K. Kobayashi and T. Saegusa, J. Am. Chem. Soc., 99, 3532 (1977).
2. Y. Ito, K. Kobayashi and T. Saegusa, Tetrahedron Lett., 1978, 2087.
3. J. T. Carlock, J. S. Bradshaw, B. Stanovnik and M. Tišler, J. Org. Chem., 42, 1883 (1977).
4. 2b-i was recrystallized from 1:1 n-hexane and ether. mp 70~72°. IR (KBr disk) 3260, 2120, 1120 cm^{-1}; NMR ($CDCl_3$ with TMS) δ 1.1~1.9 (m, 10H), 3.91 (s, 2H), 4.2 (m, 1H), 7.0~7.2 (m, 4H), 9.4 (broad, 1H).
5. 3a-ii was chromatographed on silica gel with 1:1 $CHCl_3$ and ethyl acetate (Tlc Rf=0.37). mp 205~207°. IR (KBr disk) 3400, 3250, 1615 cm^{-1}; NMR (DMSO-d_6 with TMS) δ 1.1~1.9 (m, 10H), 3.20 (broad, 1H), 3.7 (m, 1H), 6.8~7.2 (m, 3H), 7.78 (d, 1H), 7.9 (m, 1H), 11.1 (m, 1H).

   3b-i was chromatographed on silica gel with ethyl acetate (Tlc Rf=0.56). mp 178°. IR (KBr disk) 3280, 3220, 1102 cm^{-1}; NMR (DMSO-d_6 with TMS) δ 1.2~2.1 (m, 10H), 4.45 (m, 1H) 6.9~7.3 (m, 3H), 7.74 (d, 1H), 8.1 (m, 1H), 8.8 (broad, 1H), 11.2 (m, 1H).
6. 4a-i was isolated by distillation (bp 100°/0.4 mmHg). IR (neat) 1688, 1621 cm^{-1}; NMR ($CDCl_3$ with TMS) δ 0.88 (t, 3H), 1.1~1.5 (m, 4H), 3.33 (s, 2H), 3.51 (t, 3H), 7.14 (s, 4H), 7.26 (s, 1H).
7. Y. Ito, Y. Imubushi, T. Sugaya and T. Saegusa, J. Organometal. Chem., 137, 1 (1977).
8. Y. Ito, T. Konoike and T. Saegusa, J. Organometal. Chem., 85, 395 (1975).

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