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Novel Construction of 4H-2,3-Dihydro-1,3-benzothiazine Ring via Nickel(0)-Catalyzed Reaction of *o*-Iodobenzamide or *o*-Iodobenzonitrile with Thioureas

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Nickel(0) complex induced the catalytic reaction of *o*-iodobenzamide or *o*-iodobenzonitrile with thioureas giving rise to cyclized products, 4H-2,3-dihydro-2-imino-1,3-benzothiazin-4-one or 4H-2,3-dihydro-1,3-benzothiazine-2,4-diimine.

The application of transition-metal complexes to a synthesis of heterocyclic compounds has been proved to be unequivocally useful.[1)] Thioureas, which possess four reactive sites, constitute versatile starting materials for the procuring various heterocyclic compounds; however, they have been scarcely utilized in the transition metal-promoted heterocyclic syntheses.[2)] Here we will report a novel construction of 4H-2,3-dihydro-1,3-benzothiazines taking advantage of a nickel(0)-catalyzed reaction of iodoarenes with thioureas.

In the course of our study on the transition-metal catalyzed nucleophilic displacement of aryl halides,[3)] we found that *o*-iodobenzamide underwent the reaction with thiourea by the catalysis of a nickel(0) complex, generated in situ from bis(triethylphosphine)nickel(II) chloride and sodium cyanoborohydride as a reducing agent, to afford 4H-2,3-dihydro-2-imino-1,3-benzothiazin-4-one (2) in good yield. N-Substituted- or N,N'-disubstituted thioureas could be used in the place of thiourea to produce the corresponding 4H-2,3-dihydro-1,3-benzothiazine derivatives (3-5) in good yields, too; although steric hindrance decreases the reaction rates considerably. Since 1) this nickel(0) catalyzes the nucleophilic displacement of aryl iodides with thioureas under cited conditions,[4)] and 2) both nitrogen atoms of thioureas are incorporated into products (2-5), this novel ring-construction probably proceeds via an initial S-arylation (1) followed by a nucleophilic attack by the isothiuronium-nitrogen atom at the electrophilic amide-carbon atom (intramolecular amide exchange). Other electrophilic substituent like cyano group can be used in the place of amide group affording 6 as well. Iodoarenes containing an electrophilic but less co-ordinative ortho-substituent like acyl- or ester group, however, did not react with thiourea under the examined

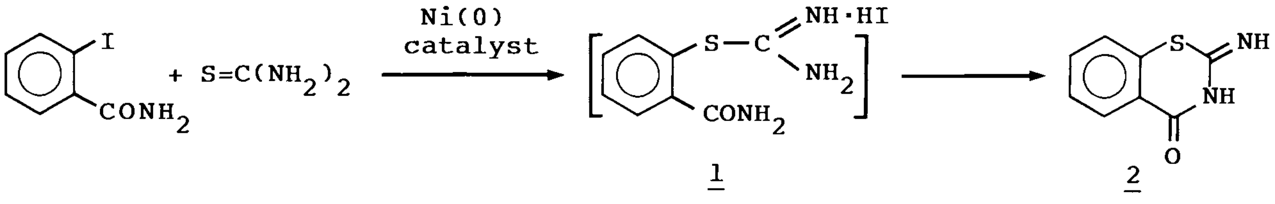
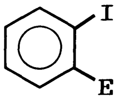
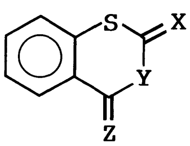


Table 1. Synthesis of 4H-2,3-Dihydro-1,3-benzothiazines[a)]

	$R^1NHC(S)NHR^2$		Time / h	Product (Yield/%[b)])
E	R^1	R^2		
$CONH_2$	H	H	4	2 (71)
$CONH_2$	CH_3	H	20	3 (85)
$CONH_2$[c)]	C_6H_5	H	5	4 (81)
$CONH_2$	CH_3	CH_3	40	5 (80)[d)]
CN	H	H	20	6 (42)[e)]
CO_2CH_3	H	H	20	-
$COCH_3$	H	H	20	-



3 X=NCH$_3$, Y=NH, Z=O

4 X=NC$_6$H$_5$, Y=NH, Z=O

5 X=Y=NCH$_3$, Z=O

6 X=Y=Z=NH

7 X=Z=O, Y=NH

a) Every runs were carried out in DMF at 60 °C under nitrogen. Molar ratio of each component (ArI/thiourea/$(PEt_3)_2NiCl_2$/$NaBH_3CN$) was 1.0/1.5/0.04/0.08.

b) Isolated yields. c) Run in NMP. d) The conversion was 45%.

e) The yield of 7 after an acidic hydrolysis of 6.

conditions. Thus, 4H-2,3-dihydro-1,3-benzothiazine-ring, which is of special pharmacological interest,[5)] is now obtained readily from a novel combination of reagents (thioureas as S,N-binucleophiles and o-iodobenzoic acid derivatives as C,C-bielectrophiles) by using a procedure of operationally very simple.

Typical procedure is as follows: A mixture of *o*-iodobenzonitrile (229 mg, 1.0 mmol), thiourea (114 mg, 1.5 mmol), $(PEt_3)_2NiCl_2$ (14.6 mg, 0.04 mmol), 1.0 M THF-solution of $NaBH_3CN$ (0.08 ml, 0.08 mmol), and DMF (0.5 ml) was stirred at 60 °C for 20 h under nitrogen. To the resulting solution, 6 N HCl (1 ml) was added. After stirring for 2 h at 80 °C, the reaction mixture was shaken with ether-brine. The ether-extract was chromatographed on a silica-gel column, affording 75 mg of 4H-2,3-dihydro-1,3-benzothiazine-2,4-dione (7) (42%). Mp 210-215 °C (lit.,[6)] 212-214 °C). Found: C, 53.44; H, 2.74; N, 7.81%. Calcd for $C_8H_5NO_2S$: C, 53.62; H, 2.81; N, 7.82%.

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