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SYNTHESIS OF ALKYL- OR ARYL-SUBSTITUTED HETELOCYCLES: NICKEL COMPLEX CATALYZED COUPLING REACTION OF HETEROCYCLIC SULFIDES AND THIOLS WITH GRIGNARD REAGENTS

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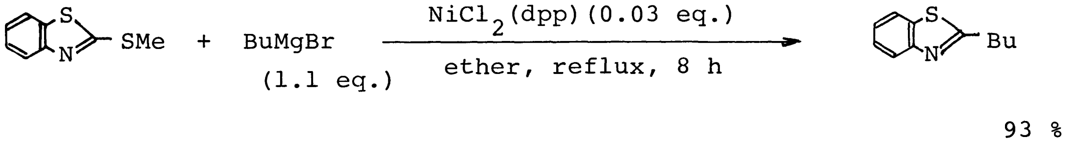
Heterocyclic sulfides and thiols react with Grignard reagents in the presence of $NiCl_2(Ph_2PCH_2CH_2CH_2PPh_2)$ to afford the cross-coupling products in high yields. The reaction of 2,2'-dipyridyl disulfide with 3-phenylpropylmagnesium bromide is also described.

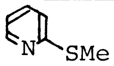
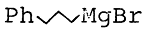
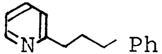
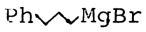
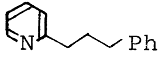
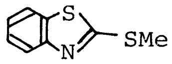
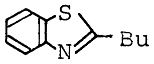
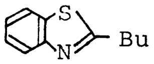
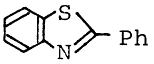
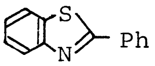
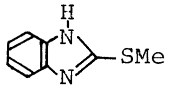
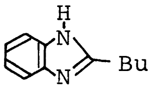
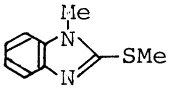
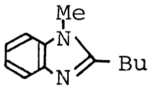
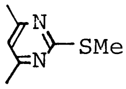
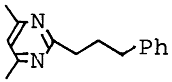
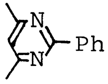
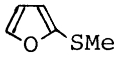
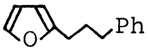
Recently we have found that alkenyl,[1)] aryl[1)] and allylic sulfides[2)] can stereospecifically couple with Grignard reagents in the presence of nickel-phosphine complexes. In this communication, we will show that the coupling reaction is applicable to the heterocyclic systems.[3)]

First, we examined the $NiCl_2(dpp)$[4)] ($dpp=Ph_2PCH_2CH_2CH_2PPh_2$) promoted coupling reaction of heterocyclic sulfides with Grignard reagents. As expected, the coupling products were obtained in high yields, except for a few cases. For example, butylmagnesium bromide reacted with 2-methylthiobenzothiazole in boiling ether in the presence of $NiCl_2(dpp)$ to give 2-butylbenzothiazole in 93 % yield.



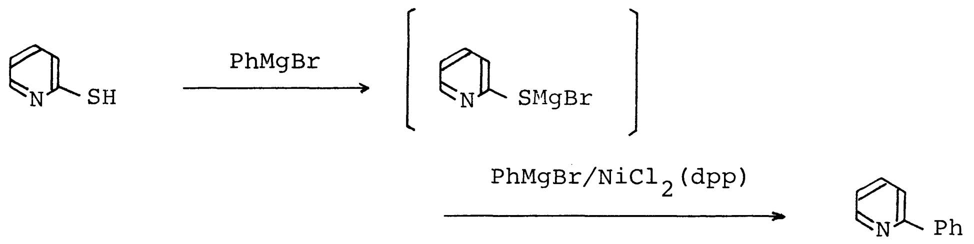
The results of the coupling reaction[5)] between a variety of heterocyclic sulfides and Grignard reagents were shown in Table 1. Runs 3 and 5 demonstrated that the reaction did not proceed without the nickel complex. By the present coupling reaction, alkyl or phenyl substituted derivatives of pyridine, pyrimidine, benzothiazole and furan were synthesized although 2-methylthiobenzimidazole and 1-methyl-2-methylthiobenzimidazole did not give the coupling products.

Table 1. Coupling Reaction of Heterocyclic Sulfides with Grignard Reagents Catalyzed by $NiCl_2$(dpp)[a]

run	Sulfide	RMgX	Product[b]	Mp(°C)[c]	Yield(%)[d]
1		PhMgBr		oil	79
2				oil	90
3				--	0[e,f]
4		BuMgBr		oil	93
5		BuMgBr		--	0[e,g]
6		PhMgBr		113-113.5	98
7		PhMgBr[j]		113-113.5	85
8		BuMgBr[k]		--	0[h]
9		BuMgBr		--	0[i]
10				oil	92
11		PhMgBr		80.5-81	94
12				oil	(55)

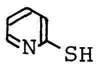
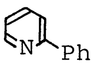
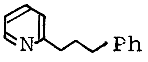
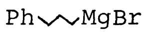
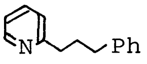
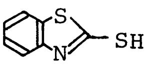
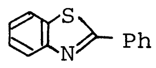
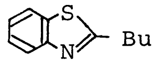
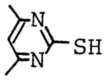
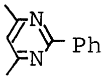
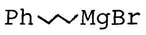
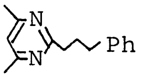
a) All of the reactions were carried out in refluxing ether for 8 h. Molar ratio of $NiCl_2$(dpp)/sulfide/RMgX is 0.03/1.00/1.1-1.5, unless otherwise noted.
b) All products gave satisfactory elemental analyses, and nmr spectra of them well agreed with the assigned structures. c) Uncorrected. d) Yields of isolated products by tlc. The number in parentheses is yield determined by glpc. e) The reactions were carried out in the absence of $NiCl_2$(dpp). f, g, h, and i) The starting sulfides were recovered in 80, 88, 77, and 88 % yields respectively. j) Excess amount (4.0 eq.) of PhMgBr was used. k) BuMgBr (2.3 eq.) was used.

Next, we examined the coupling reaction of heterocyclic thiols[6] with Grignard reagents. Similar to heterocyclic sulfides, the coupling products were obtained in high yields as expected though 2 equivalents of Grignard reagents were necessary for the coupling reaction. The reaction between 2-pyridinethiol and phenylmagnesium bromide is pictured in the next page.



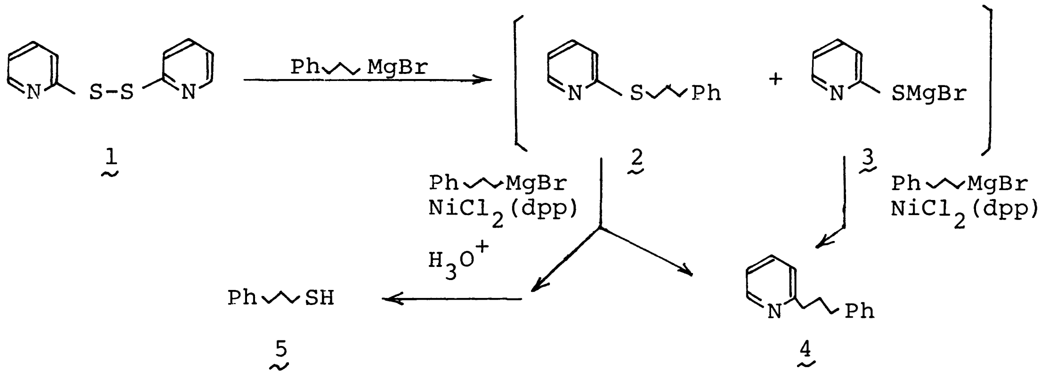
In this reaction, the magnesium salt of the thiol is assumed to be the intermediate. This assumption is supported by the reaction of 2,2'-dipyridyl disulfide shown later. Some examples of the cross-coupling[5)] of heterocyclic thiols are summarized in Table 2.

Table 2. Coupling Reaction of Heterocyclic Thiols with Grignard Reagents Catalyzed by NiCl$_2$(dpp)[a)]

run	Thiol	RMgX	Product[b)]	Mp(°C)[c)]	Yield(%)[d)]
1		PhMgBr		oil	88
2				oil	94
3				--	0[e)]
4		PhMgBr		113-113.5	79
5		BuMgBr		oil	89
6		PhMgBr		80.5-81	43[f)]
7				oil	< 8[f,g)]

a) All of the reactions were carried out in refluxing ether for 8 h. Molar ratio of NiCl$_2$(dpp)/thiol/RMgX is 0.03/1.00/2.5, unless otherwise noted. b) All products gave satisfactory elemental analyses, and nmr spectra of them well agreed with the assinged structures. c) Uncorrected. d) Yields of isolated products by tlc. e) The reaction was carried out in the absence of NiCl$_2$(dpp), and thiol was recovered in 95% yield. f) The starting thiol was not recovered. g) Contaminated with unidentified compounds.

Finally, an interesting result of the reaction of 2,2'-dipyridyl disulfide is described. In this reaction, not only the coupling product, 2-(3-phenylpropyl) pyridine (**4**, 0.88 mmol, 88%) , but also 3-phenyl-1-propanethiol (**5**, 0.43 mmol, 86%) were formed from 2,2'-dipyridyl disulfide (**1**, 0.5 mmol) and 3-phenylpropylmagnesium bromide (1.8 mmol). This result suggests the following processes. First, 3-phenylpropylmagnesium bromide reacts with **1** to give the sulfide (**2**) and the magnesium salt of thiol (**3**). Then **2** and **3** couple with the Grignard reagent by the action of NiCl$_2$(dpp) catalyst. Thus, **4** (2 mol) and **5** (1 mol) are formed from 1 mol of **1**. These processes are pictured as follows.



References and Notes

1) H. Okamura, M. Miura, and H. Takei, Tetrahedron Lett., 1979, 43.

2) H. Okamura and H. Takei, Tetrahedron Lett., 1979, 3425.

3) Generally, heterocyclic sulfides and thiols are readily available by a variety of methods and inexpensive.

4) Among the nickel catalysts, $NiCl_2$(dpp) is the most effective catalyst for the cross-coupling between simple Grignard reagents with alkenyl or aryl halides[7] and sulfides.[8]

5) A general procedure for this coupling reaction is as follows: Under an argon atmosphere, to a mixture of sulfide or thiol (1.00 mmol) and $NiCl_2$(dpp)(16 mg, 0.03 mmol) in ether (10 ml) was added a proposed amount of Grignard reagent (ca. 1.5 M ethereal solution) at room temperature. The resulting mixture was heated to reflux for 8 h. After addition of 1 M hydrochloric acid and ether followed by neutralization by sat. Na_2CO_3 aq. solution, the mixture was filtered. The organic layer was separated, washed, and dried. After removal of the solvent in vacuo, the coupling product was isolated by tlc purification.

6) Some of the heterocyclic thiols are known to exist mainly as tautomeric thione formes. In order to simplify, we deal with the compounds as thiols in this paper.

7) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, Bull. Chem. Soc. Jpn., 49, 1958 (1976); and references cited therein.

8) H. Okamura, M. Miura, K. Kosugi, and H. Takei, unpublished.

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