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Nickel-Mediated Selective Carbonylation Routes to Thiocarbamates

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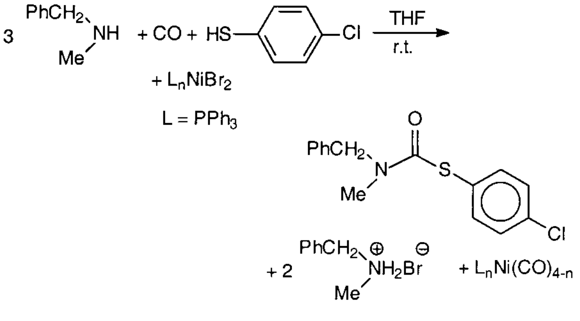
Summary: The nickel complexes Ni(PPh$_3$)$_2$X$_2$ (X = Cl, Br) have been found to be active for the selective oxidative coupling of aryl thiols with secondary amines and carbon monoxide to give thiocarbamates. With added oxygen, the reaction is catalytic, although competitive oxidation of the thiol is problematic.

Introduction

The design and development of environmentally benign processes to replace the use of phosgene have received considerable attention in recent years. Carbon monoxide is a promising candidate for the replacement of phosgene in the synthesis of acyl products, and transition metal catalysis involving carbonyl insertion reactions suggests a viable alternative. Carbonyl insertions into heteroatom-bound ligands of transition metals have been reported to generate thiolactones,[1−3] thioesters,[4] carbamates,[5] isocyanates,[6−8] and ketones.[9,10] Of more relevance to the present study is the synthesis of mixed heterosubstituted carbonyl derivatives as in urethanes recently reported by Alper.[11] Reaction of a nitroaromatic with CO in methanol solvent in the presence of palladium clay and Ru$_3$(CO)$_{12}$ leads to the direct formation of urethanes and diurethanes. In related studies, [RhCl(COD)]$_2$ was shown to catalyze carbonylation of 1,3-thiazolidines to thiazolidinones,[6] and sulfenamides undergo a palladium-catalyzed carbonyl insertion reaction to generate thiocarbamate products.[12] Recently, we reported that (PPh$_3$)$_2$PdCl$_2$ and (PPh$_3$)$_2$PdBr$_2$ are capable of reacting with amines and thiols in the presence of CO to generate thiocarbamate products.[13] Herein we report the results of our stoichiometric and catalytic studies using (PPh$_3$)$_2$NiBr$_2$ and (PPh$_3$)$_2$NiCl$_2$.

Results and Discussion

A green THF solution of (PPh$_3$)$_2$NiBr$_2$ was treated with an excess (20 equiv) of benzylmethylamine to produce a light yellow solution. Addition of a slight excess of 4-chlorobenzenethiol resulted in the formation of a reddish brown solution and a precipitate. After stirring for 17 h under 1 atm CO at room temperature, the solution became colorless and a white precipitate formed. The desired thiocarbamate was isolated in 63% yield by evaporation of solvent (eq 1).



(1)

The major side product of the reaction is the white amine hydrobromide salt which precipitates out of solution. Also detected by GC−MS were S(C$_6$H$_4$Cl)$_2$ resulting from the oxidation of the thiol, small amounts of (SC$_6$H$_4$Cl)$_2$, and triphenylphosphine sulfide. Use of (PPh$_3$)$_2$NiCl$_2$ in place of the dibromide also gave equally good yields of thiocarbamate (61%) for the same substrate. Using *N*-benzylmethylamine as the excess reagent, a range of thiols with varying substituents at the ortho and para position were investigated under the same conditions as above. The results are summarized in Table 1, showing that the reaction is amenable to a range of aromatic thiols with varying substituents. Although a reduced yield was obtained in the case of 4-fluorothiophenol, electronic effects do not seem to be very significant. Benzylmercaptan, the only aliphatic thiol investigated, gave only an 18% isolated yield (entry 9).

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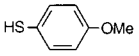
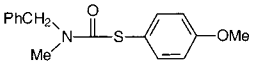
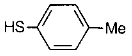
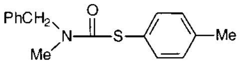
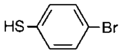
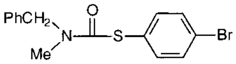
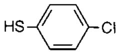
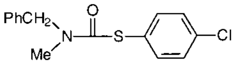
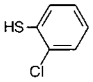
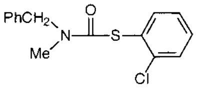
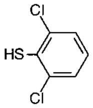
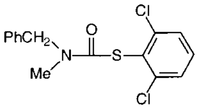
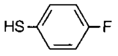
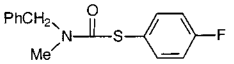
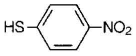
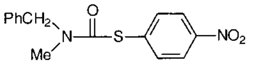
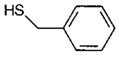
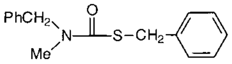
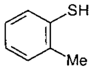
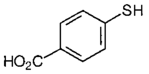
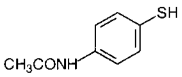
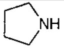
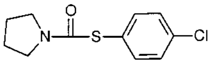
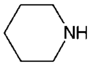
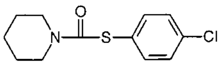
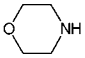
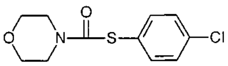
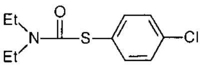
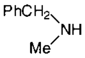
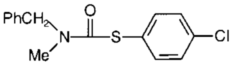
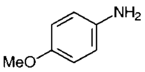
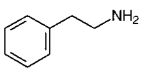
Table 1. Isolated Yields of Thiocarbamate Using *N*-Benzylmethylamine as One of the Reactants[a]

Entry	Thiol	Product	% yield
1			67
2			55
3			65
4			63
5			59
6			62
7			38
8			53
9			18
10		--	0
11		--	0
12		--	0

[a] The isolated yields are based on the amount of starting nickel complex.

Table 2. Isolated Yields of Thiocarbamate Using 4-Chlorobenzenethiol as One of the Reactants

Entry	Substrate	Product	% yield
1			66
2			50
3			53
4	Et_2NH		63
5			63
6	$PhNH_2$	--	0
7		--	0
8	Ph_2NH	--	0
9	PhNHMe	--	0
10		--	0
11	$CyNH_2$	--	0
12	Cy_2NH	--	0

To further extend the utility of this reaction, various amines were studied using 4-chlorobenzenethiol as the thiol reactant. The results are shown in Table 2. As is evident from the table, the reaction is very selective for secondary aliphatic amines. Primary and secondary aromatic amines as well as primary aliphatic amines failed to undergo this reaction. Steric factors seem to explain the lack of reactivity of dicyclohexylamine (entry

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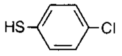
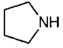
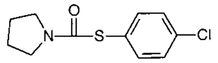
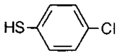
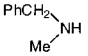
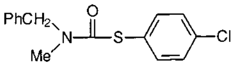
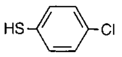
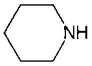
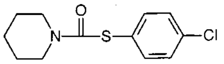
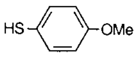
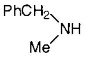
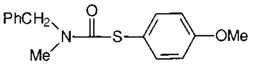
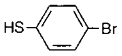
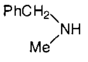
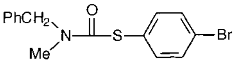
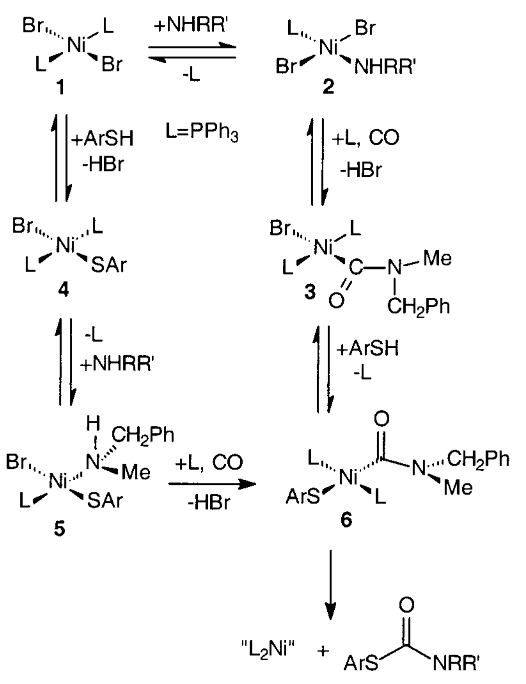
Table 3. Results of Catalytic Studies Using $(Ph_3P)_2NiBr_2$ and Air as Oxidant

Entry	Thiol	Amine	Product	GC yield[a]	Yield of disulfide
1				36(31)	61
2				24(21)	58
3				21(12)	59
4				11(6)	86
5				30(24)	60

[a] Isolated yields are shown in parentheses.

Scheme 1



12), where no color change was observed on addition of the amine to the green nickel complex.

Scheme 1 represents a plausible mechanism for the reaction based upon our detailed studies with palladium.[13] Starting from **1**, the formation of the thiocarbamate can be explained by either of the two routes involving intermediates of the type **3** or **4**. The order of addition of the amine and thiol does not alter the reaction products, suggesting rapid equilibration between the different species in solution. Addition of excess amine to a THF solution of **1** results in a rapid color change from green to light yellow, indicative of the formation of a coordination complex as in **2**. The paramagnetic nature of **1** prevents easy monitoring of the reaction by NMR spectroscopy, but a GC−MS analysis of a mixture of the two reagents shows free Ph_3P. This initially formed complex **2** can undergo CO insertion to give an amido complex **3** with elimination of HBr and recoordination of PPh_3, as seen with the palladium analogue. The hydrobromide salt of the amine precipitates out of solution. **3** generates **6** on reaction with thiol, which undergoes reductive elimination to generate a nickel(0) species and the thiocarbamate product. With excess amine present the thiol is present as the deprotonated thiolate anion. In addition, the presence of both amine and ammonium ion means that the reaction occurs under essentially buffered conditions. Alternatively, the mechanism could be viewed as one involving the initial formation of a thiolatonickel complex as in **4**, which on amine coordination and CO insertion could generate **6**, poised for reductive elimination. With the palladium system we reported earlier, complexes analogous to **2**, **3**, and **4** were either structurally characterized or detected by NMR spectroscopy.

Complex **6** in Scheme 1 undergoes reductive elimination to generate a nickel(0) species, which in the presence of CO could generate $(PPh_3)_2Ni(CO)_2$ (**7**). ^{31}P NMR spectra of the crude reaction mixture following the reaction shows three signals at δ 33.51, 31.76, and −4.78 with relative intensities of 4:1:1, respectively. Addition of an authentic sample of **7** showed enhancement of intensity for the signal at δ 33.51, confirming it as the major nickel species at the end of the reaction. The signal at δ 31.76 corresponds to $(Ph_3P)Ni(CO)_3$, and that at δ −4.78 to free PPh_3. The presence of the two nickel(0) species was further confirmed by IR spectroscopy, which showed the characteristic stretches for **7** at 2002 and 1943 cm^{-1} and those for $(Ph_3P)Ni(CO)_3$ at 2067 and 2000 cm^{-1}.[14] The dominant sulfur-containing byproduct formed in the reaction is $S(C_6H_4Cl)_2$ (60−70% of byproducts), along with small amounts of $(SC_6H_4Cl)_2$ and triphenylphosphine sulfide. The thermolysis of $Ni(SPh)_2(PEt_3)_2$ has been reported to yield PhSPh in quantitative yield[15,16] and probably accounts for the formation of the diaryl sulfide.

Catalytic Studies. The system can be made catalytic by the addition of a suitable oxidant to regenerate Ni(II) from Ni(0) and complete the catalytic cycle. An ideal system would be one where oxygen could be used as the oxidant, so that the HX would be recycled to produce H_2O, and therefore no side products would be formed in the reaction (eq 2). To test this possibility, experiments were run using catalytic amounts

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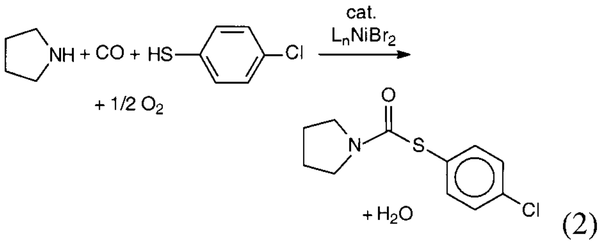

(2)

of $(PPh_3)_2NiBr_2$ (7% relative to thiol) and air as the oxidant. Table 3 summarizes the results of these studies. The complete consumption of the thiol is accompanied by a color change from reddish brown to pale yellow, upon which the system was analyzed by GC. Although there is catalytic formation of the thiocarbamate, competitive oxidation of the thiol to the disulfide accounts for most of the thiol consumption and represents a drawback of using O_2 as reoxidant. Monitoring the reaction by IR spectroscopy shows the two Ni(0) carbonyl compounds as the resting state species. H_2O is observed to grow in (3345 cm^{-1}) along with thiocarbamate (1674 cm^{-1}) during the reaction.

Conclusions

$(PPh_3)_2NiBr_2$ and $(PPh_3)_2NiCl_2$ are capable of reacting with amines and thiols in the presence of CO to generate thiocarbamate products. Superior yields of thiocarbamate are obtained with the nickel system compared with the analogous palladium system reported earlier. A catalytic synthesis is realized by using a mixture of air and CO, although the issue of competitive oxidation of the thiol remains to be satisfactorily addressed.

Experimental Section

General Methods. Most manipulations were performed under an N_2 atmosphere, either on a high-vacuum line using modified Schlenk techniques or in a Vacuum Atmospheres Corporation glovebox. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl solution. $(PPh_3)_2NiBr_2$, $(PPh_3)_2NiCl_2$, and $(PPh_3)_2Ni(CO)_2$ were purchased from Strem and used as received. CO was purchased from Air Products. The amines and thiols used in this study were purchased from Aldrich Chemical Co. and purified by standard procedures.

All ^1H, ^{13}C, and ^{31}P NMR spectra were recorded either on a Bruker AMX400 spectrometer or an AVANCE400 spectrometer. All ^1H chemical shifts are reported in ppm (δ) relative to tetramethylsilane and referenced using chemical shifts of residual solvent resonances (THF-d_8, 1.73). ^{31}P NMR spectra were referenced to external 85% H_3PO_4 (δ 0.0). GC−MS were conducted on a 5890 Series II gas chromatograph fitted with an HP 5970 Series mass selective device. All isolated thiocarbamates gave satisfactory NMR, IR, and mass spectral data.[17]

Synthesis of Thiocarbamates. For the results recorded in Tables 1 and 2, a typical experiment with entry 1 Table 1 is as follows: To 226 mg of $(PPh_3)_2NiBr_2$ (0.3 mmol) in 16 mL of dry THF in a 50 mL round-bottom flask is added 0.62 mL of *N*-benzylmethylamine (4.8 mmol) with stirring in a glovebox. The mixing of the two reagents is accompanied by a color change from green to light yellow. 4-Methoxybenzenethiol (52 mg, 0.37 mmol) is added, and a reddish brown suspension is obtained. The reaction mixture is fitted with a Schlenk adapter, the solution is freeze−pump−thaw-degassed (3×) to remove most of dissolved nitrogen, and then CO is introduced at 730−740 mm of Hg. The reaction is stirred at room temperature for 15 h (12−17 h for the various substrates), and the solution turns almost colorless with precipitation of aminehydrobromide salt. The reaction mixture is concentrated to ~2 mL, and the product thiocarbamate is isolated by preparative TLC using 20% ethyl acetate in hexane as eluent. Yield: 59 mg (67% based on $(PPh_3)_2NiBr_2$).

Catalytic Reactions. For the results recorded in Table 3, a typical experiment is as follows: To 27.5 mg of $(PPh_3)_2NiBr_2$ (0.037 mmol) and 16.0 mg of octadecane (0.063 mmol) in 20 mL of THF in a 50 mL round-bottom flask is added 0.5 mL of pyrrolidine (6.02 mmol) followed by 74.5 mg of 4-chlorobenzenthiol (0.52 mmol) with stirring. CO and air are bubbled through the solution for 4 h when the color of the solution changes from reddish brown to pale yellow. The reaction mixture is analyzed by GC, and the yields of the thiocarbamate and disulfide were determined by calibration with a sample prepared independently. The reaction mixture is then concentrated to ~2 mL, and the thiocarbamate was isolated in 33% yield based on thiol (41 mg) by preparative TLC using 20% ethyl acetate in hexane as eluent.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, IR, and mass spectral (MS) data for the different thiocarbamates. This material is available free of charge via the Internet at http://pubs.acs.org.

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