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# SYNTHESIS OF KETIMINES VIA PALLADIUM COMPLEX-CATALYZED CROSS-COUPLING OF IMIDOYL CHLORIDES WITH ORGANOTIN COMPOUNDS

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Summary: Imidoyl chlorides were successfully transformed into ketimines when treated with organotin compounds in the presence of palladium complex catalysts.

Reduction and alkylation of imidoyl chlorides into imines are important reactions of practical potential for the synthesis of β-lactam antibiotics.[1,2] Moreover, imines are useful as electrical devices like liquid crystals[3] and as synthetic intermediates which allow numerous transformations.[4] In view of these backgrounds, it is interesting to elucidate the reductive, alkylative (or arylative), and acylative reactivities of imidoyl chlorides. One of us have examined the reductive and acylative transformations into aldimines, amines,[5] α-keto imines, diazabutadienes,[6] and mesoionic oxazolones,[7] using hydrido- and acylcarbonylmetallates.

With regard to the alkylation (arylation) of imidoyl chlorides, Karady *et al.* have recommended the reaction with the cuprate reagents,[8] but the yields are poor to moderate. Although Grignard reagents can be used for this purpose,[9] the recent papers by Alper *et al.* have disclosed that the imines once formed further react with the Grignard reagents.[10] Another major drawback of Grignard reagents is that many functional groups are not tolerated in their reactions. On the other hand, unsymmetrical ketones can be synthesized from acid chlorides and organotin compounds by the palladium complex-catalyzed cross-coupling reaction which starts from the oxidative addition of acid chlorides.[11] As one of us have reported, imidoyl chloride also undergoes the oxidative addition on the low valent palladium complex.[12] Combining these precedent results, the use of organotin compounds in the presence of palladium catalysts would open up the novel and selective method for the ketimine synthesis, which will be the subject of the present communication.

$$R^1\text{-}\underset{\underset{R^2\sim N}{\|}}{C}\text{-}Cl + R^3\text{-}Sn\equiv \xrightarrow{\text{Pd catalyst}} R^1\text{-}\underset{\underset{R^2\sim N}{\|}}{C}\text{-}R^3 + Cl\text{-}Sn\equiv$$

Treatment of N-(p-methylphenyl)benzimidoyl chloride with slightly excess of tetraphenyltin in the presence of catalytic amount of various palladium complexes in ethylbenzene gave N-diphenylmethylene-p-toluidine. Biphenyl was also formed as a by-product. As Table 1 shows, tri-

phenylphosphine complexes are, in view of the yields of the ketimine, the catalysts of choice. Other palladium catalysts were either less active or less selective. We could use HMPA solvent as well, but the use of DMF or propionitrile resulted in inferior yield of the imine.

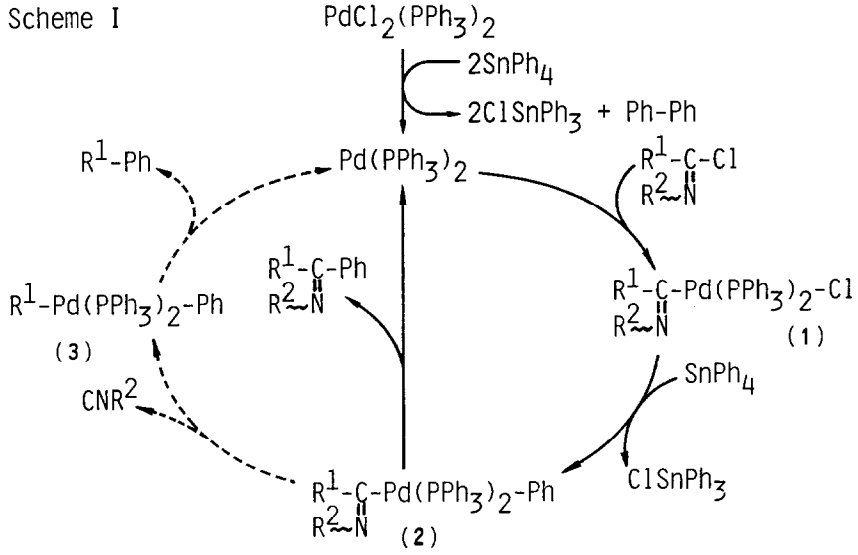
The reaction is reasonably considered to proceed *via* the sequence of elementary steps outlined in Scheme I. The imidoyl-palladium complex (**1**) formed through the oxidative addition of imidoyl chloride reacts with the tin compound, and the resulting imidoyl-phenyl-palladium complex (**2**) collapses through the reductive elimination process leading to the formation of the imine. In view of the well-known palladium complex-catalyzed decarbonylation of acid chloride,[13] it seemed likely that the biphenyl formation in the present reaction was due to the possible "de-iminocarbonylation" of the complex (**2**) into (**3**) prior to the reductive elimination. However, the biphenyl formation could not be suppressed by adding p-methylphenylisonitrile to the reaction system. In addition, biphenyl was also formed in

Table 1 N-Diphenylmethylene-p-toluidine formation from N-(p-methylphenyl)benzimidoyl chloride and tetraphenyltin[a)]

| Catalyst | Yield (%) | |
|---|---|---|
| | Ph-Ph | $p\text{-}CH_3C_6H_4N{=}CPh_2$ |
| $PdCl_2(PPh_3)_2$ | 18.1 | 70.9 |
| $(\pi\text{-}C_3H_5)PdCl + PPh_3$ | 18.1 | 58.3 |
| $(\pi\text{-}C_3H_5)PdCl + 3PPh_3$ | 16.2 | 64.9 |
| $Pd(PPh_3)_4$ | 16.2 | 59.9 |
| $PdCl_2(PPh_3)_2$ [b)] | 11.7 | 54.7 |
| $PdCl_2(PPh_3)_2$ [c)] | 20.0 | 73.6 |
| $PdCl_2(PBu_3)_2$ | 32.6 | 35.4 |
| $PdCl_2(dppb)$ [d)] | 10.2 | 13.0 |
| $PdCl_2(dppf)$ [e)] | 35.6 | 23.6 |
| $PdCl_2(PhCN)_2$ | 12.3 | 10.8 |
| 5% Pd-carbon | 11.2 | 3.3 |

a) Heated at 130°C for 15 h in the presence of 4% of catalysts. Yields are based on the imidoyl chloride, and were estimated by glc. b) The amount of the catalyst was 1%. c) The reaction was effected in the presence of $p\text{-}CH_3C_6H_4NC$ ($p\text{-}CH_3C_6H_4NC/Pd = 2$). d) Dppb = 1,4-bis(diphenylphosphino)butane. e) Dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Scheme I



the reaction of N-(p-methylphenyl)-2-thiophenecarbimidoyl chloride with tetraphenyltin, and 2-phenylthiophene which could have been formed *via* the de-iminocarbonylation was not detected. These results indicate that biphenyl was not formed from the reaction between the imidoyl chloride and tetraphenyltin, but from the latter alone. However, the formation mechanism is, at this moment, not clear.[14)]

After the initial screening, we could successfully extend the recipe by use of $PdCl_2(PPh_3)_2$ to other combinations of imidoyl chlorides and organotin compounds. The results are summarized in Table 2. A variety of imidoyl chlorides with aryl, alkyl, and heterocyclic groups on either carbon or nitrogen atom reacted with organotin compounds in a similar manner. 1-Alkenyl and 1-alkynyl tin compounds reacted faster than tetraphenyltin while tetramethyltin did slower. The reactivity of tetrabutyltin was even lower. These differences in the reactivities might be explained in terms of the ease with which the carbon-tin bond is cleaved in electrophilic substitution.[16)]

In conclusion, the cross-coupling of imidoyl chlorides with organotin compounds can be effected by the palladium catalysis. Besides the standard method of chlorination of amides, imidoyl chlorides can be synthesized by chlorination of aldimines with hypochlorites[17)] as well as the Beckmann rearrangement of ketoximes.[18)] Therefore, the new cross-coupling will be useful also for the following transformations.

$$R^1CHO \longrightarrow R^1CH{=}NR^2 \xrightarrow{R^4OCl} R^1C(Cl){=}NR^2 \xrightarrow[Pd\ cat.]{R^3Sn\equiv} R^1R^3C{=}NR^2 \longrightarrow R^1R^3C{=}O$$

$$R^1R^2C{=}O \longrightarrow R^1R^2C{=}NOH \xrightarrow{PCl_5} R^1C(Cl){=}NR^2 \xrightarrow[Pd\ cat.]{R^3Sn\equiv} R^1R^3C{=}NR^2 \longrightarrow R^1R^3C{=}O$$

Synthesis of N-diphenylmethylene-p-toluidine, general procedure: In a 10 ml flask were placed N-(p-methylphenyl)benzimidoyl chloride (230 mg, 1.00 mmol), tetraphenyltin (448 mg, 1.05 mmol), dichlorobis(triphenylphosphine)palladium (28.1 mg, 0.04 mmol), and ethylbenzene (2 ml), and were stirred under nitrogen at 130°C for 15 h. The resulting mixture was poured into aqueous solution of sodium carbonate and was extracted with ether. The ether layer was treated

Table 2 Ketimine formation from imidoyl chlorides and organotin compounds[a)]

| $R^1$-C(Cl)=N-$R^2$ | | $R^3SnR_3$ | Reaction temp. (°C) | Reaction time (h) | Yield (%)[b)] | |
|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | | | | $(C_6H_5)_2$ | $R^1R^3C{=}NR^2$ |
| 2-$C_4H_3S$[c)] | p-$C_6H_4CH_3$ | $Sn(C_6H_5)_4$ | 130 | 15 | 20.0 | 63.1 |
| $C_6H_5$ | p-$C_6H_4COOC_2H_5$ | $Sn(C_6H_5)_4$ | 130 | 15 | 14.8 | (70.0) |
| $C_6H_5$ | n-$C_4H_9$ | $Sn(C_6H_5)_4$ | 130 | 63 | 35.6 | (24.5) |
| $C_6H_5$ | p-$C_6H_4CH_3$ | $Sn(CH_3)_4$ | 130 | 15 | - | 26.7 |
| $C_6H_5$ | p-$C_6H_4CH_3$ | $C_6H_5CH{=}CHSn(n\text{-}C_4H_9)_3$ | 70 | 7 | - | (70.3) |
| $C_6H_5$ | p-$C_6H_4CH_3$ | $C_6H_5C{\equiv}CSn(n\text{-}C_4H_9)_3$ | 70 | 12 | - | (84.1) |
| $C_2H_5$ | $C_6H_5$ | $C_6H_5C{\equiv}CSn(n\text{-}C_4H_9)_3$ | 70 | 5 | - | (68.9) |

a) The reactions were run in ethylbenzene using 1.00 mmol of imidoyl chloride, 1.05 mmol of organotin compound, and 0.04 mmol of dichlorobis(triphenylphosphine)palladium. b) Determined by glc. The figures in parentheses are isolated yields. c) 2-Thienyl group.

with aqueous alcoholic solution of potassium fluoride in order to convert chlorotin species into insoluble fluorotin species,[19] filtered, washed with water, dried over magnesium sulfate, and was evaporated. The residue was subjected to preparative thin layer chromatography on sodium carbonate-treated silica gel (benzene) to give the imine (190 mg, 70.1%) and biphenyl (27.0 mg). The former was distilled (Kugelrohr) and the distillate was crystallized from methanol, mp 46.8-47.5°C (lit,[20] 48°C). IR (melt) 1615 $cm^{-1}$ (C=N). NMR ($CDCl_3$) δ 2.20 (s, $CH_3$), 6.64 and 6.96 (d, J = 8.4 Hz, phenylene protons), 7.05-7.85 (m, phenyl protons).

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