Tetrahedron Vol. 42, No. 14, pp. 3981 to 3986, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

2-ARYLPYRIDINES FROM 2-PYRIDYLCOPPER/TRIPHENYLPHOSPHINE AND IODOARENES

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(*Received in UK* 7 *March* 1986)

Abstract - 2-Arylpyridines are formed rather selectively in 50 to 80 % yields from 2-pyridylcopper and unactivated iodoarenes in the presence of one to two mol triphenylphosphine in toluene around 100 °C. The selectivity may be due to the ability of the copper(I) iodide-triphenylphosphine complex as a leaving group or may be discussed in terms of oxidative addition/reductive elimination. The unsymmetric coupling reaction may be general since the coupling of phenylcopper/triphenylphosphine with 2-iodopyridine also gives 2-phenylpyridine.

The use of arylcopper compounds is often a favourable alternative to the Ullmann biaryl synthesis for the preparation of symmetrical biaryls.[1] Unsymmetrical biaryls have sometimes been prepared *via* arylcopper compounds. For example, 2-thienylcopper reacts rather selectively with iodoarenes in quinoline or pyridine solution to give 2-arylthiophenes.[2,3] Some intramolecularly coordinated phenylcopper reagents containing a 2-(iminomethyl) group couple readily with similarly 2-substituted iodoarenes.[4,5] However, copper-halogen exchange often leads to a scrambling of groups and eventual formation of the symmetrical biaryls also,[6] the results resembling those of many attempted unsymmetrical Ullmann couplings.

Copper-halogen exchange may also complicate the coupling reaction of lithium diarylcuprates with iodoarenes, although excess cuprate, the presence of tributylphosphine or the oxidation of intermediate mixed cuprates may favour the desired product.[7,8]

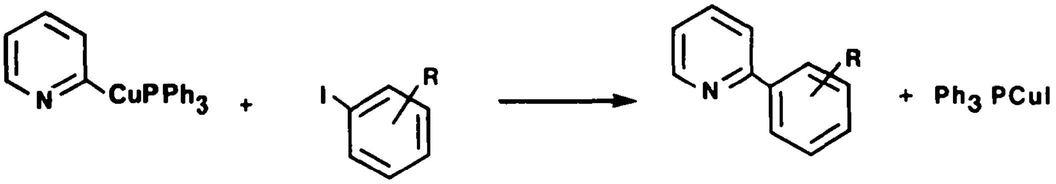
Having worked on various aspects of pyridylcopper chemistry[9-11] we have now found that reaction of 2-pyridylcopper in the presence of triphenylphosphine gives 2-arylpyridines (*1*) from non-activated iodoarenes without complicating metal-halogen exchange.

RESULTS

In preliminary experiments we reacted 2-pyridylcopper with simple iodoarenes in pyridine at 90 °C to test whether selective coupling could be achieved. Generally the results showed moderate to low yields of unsymmetrical 2-arylpyridines and considerable formation of 2,2'-bipyridyl and the other symmetric biaryl, indicating occurrence of copper-halogen exchange and subsequent scrambling. Tributylphosphine or triethyl phosphite as ligands gave similar results and also other side reactions.

With triphenylphosphine, however, the coupling turned out to be selective. With between one and three mol of triphenylphosphine present per mol of pyridylcopper the reaction with iodoarenes led to the unsymmetric 2-arylpyridines and there was little if any formation of 2,2'-bipyridyl. Toluene at 100 °C gave proper conditions for coupling with unactivated iodoarenes. Reaction in boiling tetrahydrofuran was considerably slower.

With less than one mol of triphenylphosphine we observed accentuated formation of 2,2'-bipyridyl and also formation of metallic copper, indicating thermal decomposition of the 2-pyridylcopper. With more than three mol of triphenylphosphine on the other hand the formation of 2-arylpyridine was very slow. The optimal ratio triphenylphosphine/pyridylcopper was slightly above one, the excess triphenylphosphine then being easily handled during work-up.



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Typical preparative results are summarised in Table 1. One may note that the non-activated iodoarenes reacted selectively at 100 °C. In toluene at room temperature an "activated" iodoarene such as methyl 2-iodobenzoate reacted to give the unsymmetric coupling product but also dimethyl diphenate, indicating copper-halogen exchange and subsequent scrambling. One may also note that the crowded trimethyliodobenzenes reacted at reasonable rates and with acceptable yields.

Phenylcopper/triphenylphosphine and 2-iodopyridine gave 2-phenylpyridine on reaction in toluene at 80 °C.

Table 1. Formation of 2-arylpyridines on reactions of 2-pyridylcopper/triphenylphosphine with some iodoarenes in toluene, generally at 100 °C. A slight excess of organocopper was used and the yields are based on the iodoarene.

Iodoarene	PPh_3/PyCu (PhCu)	Reaction time, h	Isolated yield, %
Iodobenzene	2	3	62
2-Methoxyiodobenzene	1	1	76
3,5-Dimethoxy-iodobenzene	1.3	1	72
2,3,4-Trimethyl-iodobenzene	1	1	58
2,4,6-Trimethyl-iodobenzene	1	2	57
Methyl 2-iodo-benzoate, R.T.	1	27	32
2-Iodopyridine + phenylcopper (80 °C)	1	0.7	74

DISCUSSION

In recent years nickel- or palladium-catalysed couplings of Grignard reagents with haloarenes have proved to be good alternatives to the Ullmann coupling for preparation of unsymmetric biaryls.[12,13] Main limitations are restrictions due to the reactivity of the Grignard reagent towards, for example, carbonyl groups and the hindrance by bulky *ortho* substituents in the haloarene.[4] A recent addition to this family of reactions is the palladium-catalysed coupling of areneboronic acids with sp^2 halides.[14]

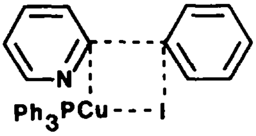
Our present results widen the scope of arylcopper reactions for biaryl synthesis. The presence of triphenylphosphine seems to stabilise 2-pyridylcopper with respect to thermal decomposition to 2,2'-bipyridyl and also to diminish the formation of the other symmetrical biaryl, which may otherwise be formed *via* copper-halogen exchange. Thus the formation of the unsymmetrical biaryl, 2-arylpyridine, is more favoured. The practical result resembles that of the couplings of the rather stable 2-thienylcopper in quinoline or pyridine solution. A corresponding stabilisation of phenylcopper by triphenylphosphine probably accounts for the good yield of 2-phenylpyridine in the reaction with 2-iodopyridine.

One may conclude that the triphenylphosphine solubilises the organocopper compounds and stabilises them with respect to both thermal dimerisation and to copper-halogen exchange. Thus, the unsymmetrical coupling to give the arylpyridine is favoured. The slow coupling in the presence of more than three mol triphenylphosphine shows that further deactivation is possible and naturally indicates that the coordinatively saturated arylcopper, e.g. PyCu-$(PPh_3)_3$, is rather unreactive.

It has been reported that phenylcopper is "moderately stabilised" and markedly solubilised by 0.3 to 3 mol triphenylphosphine.[15] Triphenylphosphine also "activates" phenylcopper for reaction with carbon dioxide.[16] A soft ligand seems to be needed for reaction between an organocopper compound and a haloarene, be it coupling or copper-halogen exchange.[8]

The detailed mechanisms of organocopper coupling and halogen-metal exchange reactions are not known, but could well involve similar or common intermediates.

Our present results indicate that the triphenylphosphine favours the direct carbon-carbon coupling at the expense of the copper-halogen exchange. One interpretation would be that the copper(I) iodide-triphenylphosphine complex provides a good leaving group from possible transition states or intermediates like *2* or the zwitterionic compound *3*.



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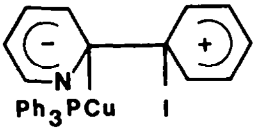

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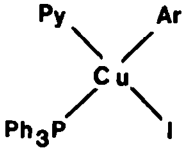
The results could also possibly be interpreted in terms of oxidative addition and reductive elimination.[17] A *cis* addition of a carbon-iodine bond in an iodoarene (Ar-I) to the 2-pyridylcopper triphenylphosphine complex, (Py-Cu PPh_3), could give two planar, isomeric copper(III) adducts, *3* and *4*. Of these, only adduct *4* with adjacent pyridyl and aryl groups should produce 2-arylpyridine on reductive *cis*-elimination. The adduct 5 should give only the thermodynamically less favoured products of copper-halogen exchange or starting materials on reductive elimination.



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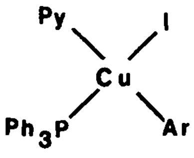

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The reactions of 2-pyridylcopper with iodoarenes thus seem to afford new possibilities for the synthesis of arylpyridines, which are interesting as chelating agents and in pharmacological studies.[18,19] We have also noted that 3-pyridylcopper gives good selective couplings with methoxyiodobenzenes.[20] The selective coupling of arylcopper compounds with iodoarenes in the presence of triphenylphosphine may thus be a general reaction, which we hope to exploit further.

EXPERIMENTAL

Organometallic reactions were run under nitrogen. Tetrahydrofuran, ether and toluene were distilled from sodium benzophenone ketyl. ^{1}H-NMR spectra were recorded on a Bruker WH 270 instrument, benzene-d_6 giving better resolution than chloroform-*d* solutions. Reaction mixtures from the arylcopper reactions were filtered, and hydrolysed in aqueous ammonium chloride/ammonia with dichloromethane added. Products were extracted with 1.5 M hydrochlorid acid. After basification (ammonia), re-extraction and evaporation of the solvent the residues were flash-chromatographed or short-path-distilled. The purity of products were checked by GLC (HP 5880 A) and TLC. Mass spectra were recorded on a Finnigan 1200 GC-MS instrument (70 eV).

2-Pyridylcopper. 2-Pyridyllithium was prepared in ether (25 ml) at -70 °C from 2-bromopyridine (40 mmol, Fluka) by addition of butyllithium (40 mmol, Fluka) in hexane which was allowed to sweep the cooled glass surface before entering the stirred solution. After ten min. a solution of copper(I) iodide (43 mmol, Fluka) in ether (25 ml) and dimethyl sulfide (25 ml) was added in a similar fashion. After ten min. stirring the cooling bath was removed and the yellowish mixture, reaching ambient temperature, was transferred to a Schlenk filtration tube. After filtration the precipitate was washed with ether (2x15 ml), THF (15 ml) and again with ether (2x15 ml). The yellow solid was dried in vacuum to give 5.27 g pyridylcopper, 94 % yield. Portions of 2-pyridylcopper could be transferred from the storage vessel to a nitrogen-filled reaction vessel with a spoon. Preferably 2-pyridylcopper should, however, be wetted with ether before handling to prevent friction-induced decomposition. It can be stored under nitrogen at room temperature but should be consumed within a few days. When heated 2-pyridylcopper decomposes at 100-135 °C forming 2,2'-bipyridyl.

2-(3,4-Dimethoxyphenyl)pyridine. 2-Pyridylcopper (6.8 mmol) was mixed with triphenylphosphine (13 mmol) and toluene (10 ml). 3,4-Dimethoxyiodobenzene (5 mmol) was added and the heterogeneous mixture was heated to 100 °C and stirred for 5 h. After hydrolysis and work-up the product was recrystallised from light petroleum to give 2-(3,4-dimethoxyphenyl)pyridine as white needles, m.p. 72-74 °C in 72 % yield, lit.[21] m.p. 76-78 °C. Found: C 72.6; H 6.1; N 6.4. Calc. for $C_{13}H_{13}NO_2$: C 72.5; H 6.1; N 6.5. ^{1}H-NMR (benzene-d_6): 8.51 (1H, m), 7.98 (1H, d, 2.1 Hz), 7.63 (1H, dd, *J* 8.3 and 2.1 Hz), 7.44 (1 H, dm, *J* 8.0 Hz), 7.20 (1H, m), 6.72 (2H, m), 3.56 (3H, s) and 3.45 (3H, s). MS (*m/Z*): 215 (M^+, 100 %), 200 (25), 184 (24), 172 (42).

2-(2-Methoxyphenyl)pyridine. 2-Pyridylcopper (6 mmol) and triphenylphosphine (6.1 mmol) were mixed with toluene (10 ml). 2-Iodomethoxybenzene (4.5 mmol) was added and the mixture stirred at 100 °C for one h. After hydrolysis and work-up the basic material was flash chromatographed (light petroleum, b.p. 40-60 °C, 0.6 M triethylamine) to give 2-(2-methoxyphenyl)pyridine as a colourless oil, in 76 % yield (0.63 g); lit.[22] b.p. 96-99 °C. Found: C 77.4; H 6.0; N 7.4; O 9.7. Calc. for $C_{12}H_{11}NO$: C 77.8; H 6.0; N 7.5; O 9.7. ^{1}H-NMR (benzene-d_6): 8.64 (1H, m), 8.28 (1H, dd, *J* 1.8 and 7.6 Hz), 7.88 (1H, dm, *J* 8.0 Hz), 7.25-7.10 (2H, m), 6.99 (1H, m) 6.69 (1H, m), 6.63 (1H, dd *J* 8.2 and 0.9 Hz), 3.28 (3H, s). MS: 185 (M^+, 63 %), 154 (94), 80 (100).

Methyl 2-(2-pyridyl)benzoate. A mixture of 2-pyridylcopper (9.6 mmol) triphenylphosphine (10 mmol) and methyl 2-iodobenzoate (6.4 mmol) in toluene was stirred for 27 h at room temperature. Hydrolysis, work-up and short-path distillation of basic material (160 °C/100 Pa) gave methyl 2-(2-pyridyl)benzoate (0.43 g) as an oil in 32 % yield (compare ref. 18). Found: C 73.1; H 5.2; N 6.6; O 15.1. Calc. for $C_{13}H_{11}NO_2$: C 73.2; H 5.2; N 6.6; O 15.01. ^{1}H-NMR (benzene-d_6): 8.5 (1H, m), 7.76 (1H, dm, *J* 8 Hz), 7.37 (1H, dm, *J* 7.2 Hz), 7.15-7.0 (4H, m), 6.68 (1H, m), 3.40 (3H, s). MS: 213 (M^+, 3 %), 198 (16), 182 (100), 154 (17). According to GC and GC-MS significant amounts of dimethyl diphenate had also been formed.

2-(2,3,4-Trimethylphenyl)pyridine. 2-Pyridylcopper (8.9 mmol) and triphenylphosphine (9 mmol) were mixed with toluene (10 ml). 2,3,4-Trimethyliodobenzene (6 mmol) was added and the mixture was stirred at 100 °C for one h. The basic material obtained after hydrolysis and work-up was flash chromatographed (light petroleum, b.p. 40-65 °C, 0.3 M triethylamine) to give 2-(2,3,4-trimethylphenyl)-pyridine (0.68 g) as an oil in 57 % yield. Found: C 85.5; H 7.8; N 6.8. Calc. for $C_{14}H_{15}N$: C 85.2; H 7.7; N 7.1. ^{1}H-NMR (benzene-d_6): 8.61 (1H, dm, *J* 4.6 Hz), 7.25 (1H, d, *J* 7.7 Hz), 7.17-7.10 (2H, m), 6.98 (1H, d, *J* 7.7 Hz), 6.70 (1H, m), 2.27 (3H, s), 2.13 (3H, s), 1.99 (3H, s). MS: 197 (M^+, 33 %), 196 (100), 181 (34), 167 (11) and 152 (6).

2-(2,4,6-Trimethylphenyl)pyridine. 2-Pyridylcopper (4.95 mmol) and triphenylphosphine (5 mmol) were mixed with 10 ml toluene. 2,4,6-Trimethyliodobenzene (4 mmol) was added and the mixture was stirred at 100 °C for two h. After hydrolysis and work-up the basic material was flash chromatographed (light petroleum, 0.3 M triethylamine) to give 2-(2,4,6-trimethylphenyl)pyridine (0.45 g) as a colourless oil in 57 % yield. Found: C 85.4: H 7.7; N 6.9. Calc. for $C_{14}H_{15}N$: C 85.2; H 7.7; N 7.1. ^{1}H-NMR (benzene-d_6): 8.65 (1H, dm, *J* 4.6 Hz), 7.20 (1H, m), 6.93 (1H, m), 6.89 (2H, s), 6.76 (1H, m), 2.21 (3H, s), 2.08 (6H, s). MS: 197 (M^+, 34 %), 196 (100), 181 (25), 167 (7) and 152 (5).

2-Phenylpyridine. 2-Pyridylcopper (9.5 mmol) and triphenylphosphine (10 mmol) were mixed in toluene (20 ml). Iodobenzene (5 mmol) was added and the mixture was stirred at 100 °C for two h. After hydrolysis and work-up the basic material was short-path distilled (150 °C/100 Pa) to give 2-phenylpyridine (0.48 g) as a colourless oil in 62 % yield. GLC, NMR and GC-MS data were identical with those of a commercial sample of 2-phenylpyridine (EGA).

2-Phenylpyridine from phenylcopper and 2-iodopyridine. Phenyllithium (10 mmol) in ether (15 ml) was cooled to -70 °C. Copper(I) iodide (10 mmol) was dissolved in dimethyl sulfide (6 ml) and ether (6 ml) and the resulting solution added to the phenyllithium solution. A yellow precipitate formed when the temperature was increased. Upon reaching room temperature the precipitate was washed with ether (2x15 ml) leaving a bright-yellow solid. Triphenylphosphine (10 mmol) and toluene (18 ml) were added and a yellow to yellow-green solution was formed. 2-Iodopyridine (4 mmol) was added and the solution was stirred at 65-80 $^{\circ}C$. A yellow-white precipitate appeared after a few minutes. After 40 min. the mixture was filtered and worked up. Short-path distillation of basic material (150 $^{\circ}C$/100 Pa) gave 2-phenylpyridine (0.46 g) in 74 % yield, identical with an authentic specimen.

ACKNOWLEDGEMENTS

The work has been supported by the Swedish National Board for Technical Development. Some preliminary experiments were performed by Mr. Göran Leibertz. Dr. David Tanner kindly checked the English of the MS. The work has been greatly facilitated by a grant for the mass spectrometer from the Swedish Council for Planning and Coordination of Research.

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