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CONJUGATE ADDITION WITH 2-PYRIDYLCOPPER AND LITHIUM 2-PYRIDYLCUPRATES

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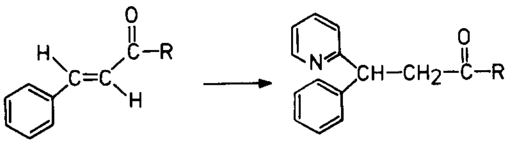
Abstract—2-Pyridylcopper/dibutyl sulfide, 2-pyridylcopper/tributylphosphine, lithium di(2-pyridyl)cuprate and lithium (2-pyridyl)(phenyl)cuprate all add the 2-pyridyl group to 4-phenyl-3-buten-2-one in good yields. The cuprates also add the 2-pyridyl group to ethyl 3-phenylpropenoate.

2-Pyridylcopper compounds have been reported as intermediates in the oxidative coupling to 2,2'-bipyridyls.[1,2] In this work we have examined some 2-pyridylcopper reagents in conjugate addition[3] to a typical enone, 4-phenyl-3-buten-2-one, and to an enoate, ethyl 3-phenylpropenoate. The reagents were prepared from 2-pyridyllithium and copper-(I) iodide complexed with dibutyl sulfide or tributylphosphine.[4]



R: $-CH_3$, $-OC_2H_5$

Equivalent amounts of 2-pyridyllithium and copper iodide/dibutyl sulfide gave 2-pyridylcopper as a yellow solid. When the enone was added to this mixture a fast reaction took place giving the conjugate addition product, 4-phenyl-4-(2-pyridyl)-2-butanone. With the enoate, no reaction took place.

The pyridylcopper could also be collected and washed with ether to remove dibutyl sulfide and lithium salts. The "lithium-halide-free" pyridylcopper did not react with the enone.

Addition of an extra equivalent of 2-pyridyllithium or phenyllithium to washed or non-washed 2-pyridylcopper gave homogeneous solutions which we regard as lithium dipyridylcuprate and lithium (2-pyridyl)(phenyl)cuprate reagents, respectively. On reaction with enone or enoate these give yellow precipitates, apparently pyridylcopper and phenylcopper, respectively.

After work up, the conjugate addition products, 4-phenyl-3-(2-pyridyl)-2-butanone and ethyl 3-phenyl-3-(2-pyridyl)-propenoate respectively, were isolated in good yields. 2-Pyridylcopper-tributylphosphine complex was obtained in homogeneous ether solution from 2-pyridyllithium and an equimolar amount of CuI/PBu_3. On addition of the enone, a fast reaction took place, while no reaction took place with the enoate.

The yields of conjugate addition products are summarized in Table 1 and show that the cuprates give better yields in conjugate addition to the enone and that they also add a pyridyl group to the less reactive enoate. Lithium iodide is not necessary for the cuprates to react.

Table 1. Conjugate addition of 2-pyridylcopper reagents to 4-phenyl-3-buten-2-one (1) and ethyl 3-phenylpropenoate (2)

Substrate(S)	Reagent(R)	Ratio R/S	Product	Isol. yield %
<u>Enone</u>,1	$PyCu\cdot SBu_2$,LiI	1.2	$PhPyCHCH_2COCH_3$	49
	$LiPy_2Cu$,LiI	1.0		85
	$LiPy_2Cu$	1.1		74
	LiPyPhCu,LiI	1.2		81
	LiPyPhCu	1.1		72
	$PyCu\cdot PBu_3$,LiI	1.1		73
	PyCu	1.1		0
<u>Enoate</u>,2	$PyCu\cdot SBu_2$,LiI	2.0	$PhPyCHCH_2COOC_2H_5$	0
	$LiPy_2Cu$,LiI	2.0		82
	LiPyPhCu,LiI	2.0		85
	$PyCu\cdot PBu_3$,LiI	2.0		0

For the complexed 2-pyridylcopper reagents lithium iodide is essential for addition to occur.[5] In spite of their lower reactivity and the moderate reaction yields as compared to the cuprates, they can still be useful due to the efficient utilization of organolithium reagents.

The preference of the mixed cuprate LiPyPhCu to transfer the pyridyl group to an α,β-unsaturated carbonyl compound is synthetically useful.[6]

Recent work on the mechanism of the reaction of lithium dimethylcuprate with α,β-unsaturated ketones[7] suggests the transient formation of a trialkyl copper(III) species which rearranges and transfers a Me group to the β carbon of the carbonyl compound. If this model holds for mixed arylcuprates such as LiPyPhCu, there are still questions to be answered as to why the pyridyl group is transferred in preference to the phenyl group. Further work is in progress to study the properties and reactions of 2-pyridylcopper.

In conclusion, the 2-pyridylcopper reagents investigated are shown to be useful for the direct conjugate addition of a pyridine ring to a substrate. Further, the formation of acid-extractable pyridyl derivatives simplifies the work up procedure otherwise necessary when neutral addition products have been formed using phosphine- or sulfide-complexed organocopper reagents.[6]

EXPERIMENTAL

All operations and reactions were performed under dry N_2. All chemicals were supplied by Fluka or Merck. Ether was distilled from sodium benzophenone ketyl. Isolated products were distilled on a short path/Kugelrohr distillation apparatus. Yields are based on the substrates.

2-*Pyridyllithium*. A soln of 2-bromopyridine (11 mmol) in ether (10 ml) was cooled to −70°. BuLi (11 mmol) was added and the resulting deep-red soln was stirred for 5 min before use. 2-Pyridyllithium was also prepared using phenyllithium, added at −25°.

Compound $LiPy_2Cu$. Copper(I) iodide (5.5 mmol) was dissolved in dibutyl sulfide (11 mmol). Ether (15 ml) was added and the soln was cooled to 0°. The soln of 2-pyridyllithium (11 mmol) was added by means of a syringe. The dark soln was stirred for 15 min before use.

Compound LiPyPhCu. Copper(I) iodide (11 mol) was dissolved in dibutyl sulfide (22 mmol). Ether (15 ml) was added and the soln was cooled to 0°. The soln of 2-pyridyllithium was added. A yellow-brown ppt was formed. After stirring for 15 min phenyllithium was added until Gilman test I[8] was positive. The soln was stirred for 15 min before use.

Alternatively the ppt obtained was centrifuged and washed twice with ether before addition of phenyllithium.

Compound $PyCu \cdot SBu_2$. Copper(I) iodide (11 mmol) was dissolved in dibutyl sulfide (22 mmol). Ether (30 ml) was added and the soln was cooled to 0°. The soln of 2-pyridyllithium (11 mmol) was added and the mixture obtained was stirred for 15 min before use.

Compound $PyCu \cdot PBu_3$. Copper(I) iodide (11 mmol) was dissolved in tributylphosphine (24 mmol). Ether was added and the soln was cooled to −70°. The soln of 2-pyridyllithium (11 mmol) was added, and the homogenous soln was stirred for 15 min before use.

Conjugate addition

General. A soln of the substrate in ether (3 ml) was added dropwise to the reagent, the amount being chosen from the ratios shown in Table 1.

Cuprates. The enone was added at 0°. A fast reaction took place and gave a yellow ppt. The mixture was hydrolysed after 20 min with aqueous ammonia/ammonium chloride. The enoate was added at room temp., and the mixture was hydrolysed after 1 hr.

Pyridylcopper complexes. The enone was added at −70° and the temp. was raised slowly (20 min) to 0° before hydrolysis. No reaction occurred with the enoate even at room temp.

Work up. Following hydrolysis, the ether layer was extracted twice with 2M HCl. This aqueous phase was made basic with aqueous ammonia and extracted twice with ether. After drying and evaporation, the residue was distilled at 140–160°/100 Pa.

With ether solns containing addition product and tributylphosphine a fraction of the ether soln was stirred with water (25 ml) and the mixture was titrated with 0.1 M H_2SO_4.[9] From the plot of pH vs volume added a pH value of 3.5 was chosen for the separation of the conjugate addition product from the mixture.

Products. 4-Phenyl-4-(2-pyridyl)-2-butanone,[10] a colourless oil, ^1H NMR (270 MHz, $CDCl_3$) δ 8.50 (m, 1H), 7.48 (m, 1H), 7.27–7.00 (m, 7H), 4.67 (dd, 1H, $J = 5.8$ and 8.9 Hz), 3.69 (dd, 1H, $J_{vic} = 8.9$ Hz, $J_{gem} = 16.8$ Hz), 2.95 (dd, 1H, $J_{vic} = 5.8$ Hz, $J_{gem} = 16.8$ Hz), 2.12 (s, 3H). *m/e* 225 (M^+), 224, 210, 182 (100%), 167.

Ethyl 3-*phenyl*-3-(2-*pyridyl*)*propanoate*,[11] a colourless oil, ^1H NMR (270 MHz, $CDCl_3$) δ 8.55 (m, 1H), 7.51 (m, 1H), 7.34–7.03 (m, 7H), 4.63 (dd, 1H, $J = 6.9$ and 8.9 Hz), 4.03 (q, 2H, $J = 7.0$ Hz), 3.44 (dd, 1H, $J_{vic} = 8.8$ Hz, $J_{gem} = 16.1$ Hz), 2.97 (dd, 1H, $J_{vic} = 6.9$ Hz, $J_{gem} = 16.0$ Hz), 1.11 (t, 3H, $J = 7.0$ Hz). *m/e* 255 (M^+), 254, 210, 182, 167, 155 (100%).

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