A REGIOSPECIFIC SYNTHESIS OF DIPHENYL-4-PYRIDYLCARBINOL[1]

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Abstract - A regiospecific synthesis of diphenyl-4-pyridylcarbinol based on the reaction of benzophenone with 4-cyanopyridine in the presence of sodium [or calcium, lithium and samarium (II)] is reported.

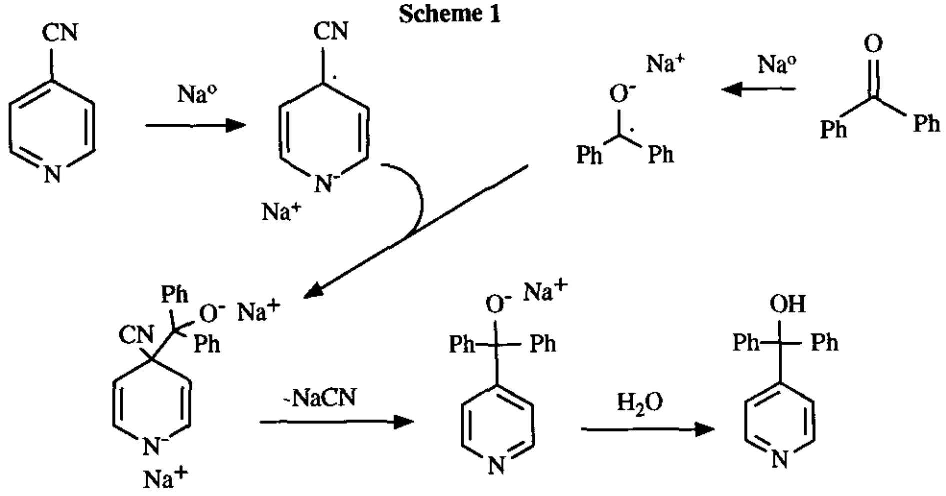
α,α-Disubstituted pyridylcarbinols have been prepared chiefly by two approaches, one involves attack at a ring carbon atom (e.g.Emmert,[2] Hammick,[3] or organometallic reactions[4]) the other transformation of a carbon substituent already present.[5] Work in this area has been driven to a large extent by the importance of 2- and 4-pyridylcarbinols as intermediates in the synthesis of antihistamines (e.g. azacyclonol) (**1**). We report that 4-pyridyldiphenylcarbinol (**2**), a precursor of azacyclonol, is formed cleanly in 70% yield by heating 4-cyanopyridine, benzophenone, and metallic sodium at reflux in xylene.[6] The product was isolated by filtration after work-up with addition of water and has physical and spectral characteristics consistent with those previously reported.[7]

We propose that this reaction takes place by a radical coupling process (Scheme 1). Precedence for this comes from work by Vittimberga and his co-workers who have obtained pyridylcarbinols from the reaction of diphenylketyl radicals (photochemically generated from benzophenone[8] and thermally generated from benzopinacol[9]) with 4-cyanopyridine.

[+] Deceased

The high yield and regioselectivity in the reaction we report compared with the Emmert reaction is attributable to the effect of the cyano substituent in stabilizing the intermediate radical and acting as a good leaving group.

Scheme 1

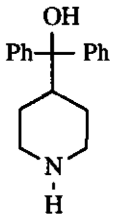


We have studied the scope of this reaction by varying the ketone, the metal used, and the position of the cyano group in the pyridine ring (Table 1). Lithium and calcium did not effect reaction at reflux in xylene as did sodium, the only one of these three metals that is molten at xylene reflux temperature. A small yield of **2** was obtained using samarium (II) iodide. Sodium, lithium and calcium were effective with liquid ammonia as the solvent for production of **2**, although in lower yield. 2-Cyanopyridine undergoes a comparable reaction to the 4-isomer. However, as expected the 3-cyano group does not participate in this reaction. Extension of this reaction of 4-cyanopyridine to other ketones has some limitations. Heating 4-cyanopyridine, acetophenone, and sodium at reflux in xylene gave many products arising from aldol condensation.

In conclusion, we have reported a useful reaction which shows potential for the preparation of 2- and 4-diarylpyridylcarbinols.

Table 1 Treatment of Cyanopyridines with Benzophenones in the Presence of a Metal

Cyanopyridine	Ketone	Metal	Proc.	Product	Yield (%)
4-	benzophenone	sodium	A	**2**	70
4-	benzophenone	lithium	A	**2**	trace
4-	benzophenone	calcium	A	**2**	-
4-	benzophenone	sodium	B	**2**	28
4-	benzophenone	lithium	B	**2**	47
4-	benzophenone	calcium	B	**2**	45
4-	benzophenone	samarium iodide	C	**2**	10
4-	Michler's ketone	sodium	A	**3**	10
4-	4-methoxy-benzophenone	sodium	A	**4**	24
2-	benzophenone	sodium	A	**5**	70



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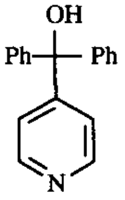

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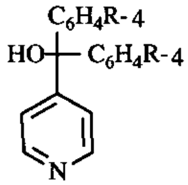
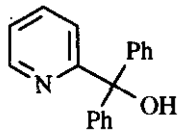


R = NMe_2 (3)
R = H, OMe (4)



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EXPERIMENTAL

4-Cyanopyridine used was manufactured at Reilly. Benzophenone and all other ketone equivalents were purchased from Aldrich. Sodium metal and xylene used were technical grade materials. Liquid ammonia used was a commercial grade material.

A typical procedure **A** involved heating 4-cyanopyridine (10.5 g, 0.1 mol) and benzophenone (18.2 g, 0.1 mol) in xylene (250 ml) together with small pieces of sodium metal (5.0 g, 0.22 mol) at reflux for 3 h. On work-up with water after cooling a precipitate was obtained which was filtered and washed with acetone. Crystallized from pyridine gave diphenyl-4-pyridylcarbinol (18.3 g, 70%).

Di-(4-N,N-dimethylphenyl)-4-pyridylcarbinol **(3)** (3.5 g, 10%) mp 125°C (lit., 123-125°C).[10]

Phenyl-4-Methoxyphenyl-4-pyridylcarbinol **(4)** (7.0 g, 24%) mp 205°C (lit., 200-204°C).[11]

Diphenyl-2-pyridylcarbinol **(5)** (18.3 g, 70%) mp 105°C (lit., 104-105°C).[2c]

A typical procedure **B** involved stirring 4-cyanopyridine (10.5 g, 0.1 mol) and benzophenone (18.2 g, 0.1 mol) in liquid ammonia (250 ml) together with small pieces of sodium metal (5.0 g, 0.22 mol) for 1 h. On work-up with toluene and water a precipitate was obtained which was filtered and washed with acetone. Crystallized from pyridine gave diphenyl-4-pyridylcarbinol (7.3 g, 28%).

Procedure **C** involved heating 4-cyanopyridine (0.52 g, 0.005 mol) and benzophenone (0.91 g, 0.005 mol) in THF (25 ml) together with samarium diiodide (4.0 g, 0.01 mol) in THF (100 ml) at 30°C for 3 h. On work-up with aqueous $NaHCO_3$ gave a precipitate which was filtered off. The filtrate was extracted with methylene chloride and on evaporation of the solvent gave a solid which crystallized from pyridine gave diphenyl-4-pyridylcarbinol (0.13 g, 10%).

REFERENCES AND NOTES

1. ***Dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday.***

DEMUT

Seh ich die Werke der Meister an,
So seh ich das, was sie getan;
Betracht ich meine Siebensachen,
Seh ich, was ich hätt sollen machen.

-J. W. von Goethe

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6. Patent has been filed for this process. R. Murugan, E. F. V. Scriven, and G. L. Goe, International Application published under PCT, WO92/19596, 12 November, 1992.

7. The melting point of **2** obtained was 238-240°C agreeing with the literature melting point of diphenyl-4-pyridylcarbinol (235°C).[3,5] The ^{1}H-nmr of **2** agreed with that reported in literature [T. J. Kress and L. L. Moore, *J. Heterocycl. Chem.*, 1972, **9**, 1161].

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