A Facile and Efficient Formylation of Grignard Reagents

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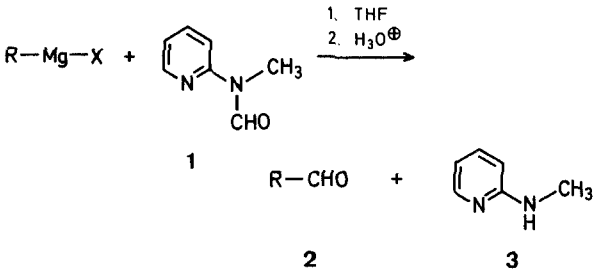
In recent years a number of methods have been reported which convert Grignard reagents to aldehyde precursors and after a subsequent step release the free aldehyde[1]. We wish to report an efficient one-step reaction which results in direct formylation of a variety of Grignard reagents using the novel reagent, **1**.



The latter is prepared in large quantity from commercially available 2-aminopyridine in two simple operations and is regenerated as the *N*-methyl derivative **3** in equally high yields. The reaction is carried out by simply adding the Grignard reagent to a solution of **1** in tetrahydrofuran at 0° and then quenched after a few minutes in dilute aqueous acid. The aldehydes **2** are obtained in high yield in generally high states of purity. The examples in the Table indicate the effectiveness of this method for aryl, alkyl, vinyl, and acetylenic Grignard reagents. Many of the earlier techniques do not exhibit this general utility. Furthermore, the previous methods invariably lead to an aldehyde in its acetal, aminal, or thioacetal form which must be cleaved in a separate synthetic operation frequently causing aldehydic decomposition or other modes of product loss.

Although Grignard reagents have been reported to undergo formylation with dimethylformamide[2], the presence of the extra ligand (pyridyl nitrogen) and the ready formation of a six-membered chelate **4** prohibits release of the aldehyde

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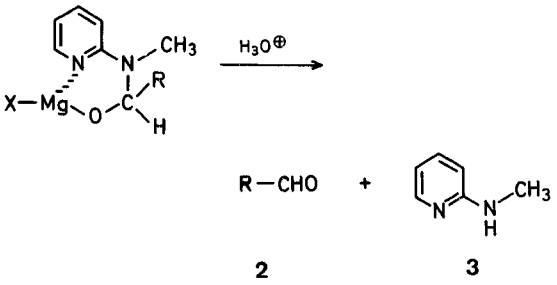
Table. Conversion of Grignard Reagents to Aldehydes **2**

R—Mg—X[a]	Yield [%][b] of R—CHO	b.p./torr	I.R. (film) ν_{max} [cm^{-1}]	^{1}H-N.M.R. δ [ppm]
C_6H_5—Mg—Br	72	62–66°/10	1710	($CDCl_3$) 10.0 (s, CHO)
1-naphthyl-Mg—Br	76	84–89°/0.05	1690	(CCl_4) 10.24 (s, CHO)
C_6H_5—CH_2—CH_2—MgBr	75	58–61°/1	1730	($CDCl_3$) 9.80 (t, CHO)
C_6H_5—CH_2—Cl	80	75–80°/10	1710	(CCl_4) 9.67 (t, CHO)
C_6H_5—CH_2—$CH(CH_3)$—Mg—Br	81	51–54°/0.05	1740	(CCl_4) 9.70 (d, CHO)
C_6H_5—C≡C—Mg—J	75	69–70°/1.5	1665	($CDCl_3$) 9.47 (s, CHO)
C_6H_5—CH=CH—Mg—Br	70	73–77°/1	1690	($CDCl_3$) 9.67 (d, CHO)

[a] All reactions performed on a 50 mmol scale.

[b] Yield of isolated aldehyde of purity >95% as determined by G.L.C. analysis (conditions: 10% UCW on AW Chrom. W 60–80 mesh, 6′ × $^1/_8$″ alumina, program 110–200°).

under the reaction conditions. This necessarily protects the aldehydic product from further reaction with Grignard reagent. A similar concept has been described by Mukaiyama[3] in the reaction of Grignard reagent with *S*-(2-pyridyl)-thioates to form ketones.



2 **3**

Preparation of 2-(*N*-Methyl-*N*-formyl)-aminopyridine (1):
2-Aminopyridine (94.1 g, 1.0 mol) is added to phenyl formate (153 g, 1.4 mol) and the mixture stirred at room temperature for 23 h (drying tube). Phenol and excess phenyl formate are removed in vacuo (75–125°/10 torr) and the residue distilled to give 2-(*N*-formyl)-amino pyridine; yield: 106.8 g (99%); b.p. 108–118°/0.05 torr; m.p. 72–73°[4] (pentane).

The formamide is methylated as follows. A solution of potassium *t*-butoxide (33.7 g, 0.30 mol) in tetrahydrofuran (500 ml) under nitrogen is treated with the formamide from above (29.1 g, 0.27 mol) and the mixture stirred at room temperature for 15 min and then 30 min at reflux temperature. The suspension is then cooled to room temperature and methyl iodide (18.7 ml, 0.30 mol) is added. The mixture is heated under reflux, with stirring for 18 h, filtered and the white solid washed with tetrahydrofuran. The combined clear solution is then evaporated leaving a yellow oil which is distilled to give **1**; yield: 26.3 g (80%); b.p. 71–72°/0.05 torr.

I.R. (film): $\nu_{max} = 1690\,cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.35$ (s, 3H); 7.12 (m, 2H); 7.74 (d of t, 1H); 8.38 (m, 1H); 9.30 ppm (s, 1H).

General Procedure for Formylation of Grignard Reagents:
The Grignard reagent (50 mmol) in tetrahydrofuran or ether (20 ml) is added dropwise to a cooled (ice-bath) solution of **1** (45 mmol) in tetrahydrofuran (50 ml). The disappearance of **1** is easily monitored by T.L.C. (silica gel, ethyl acetate). The mixture is stirred an additional 10 min and then poured into cold 5% hydrochloric acid (100%). The aqueous acidic layer is extracted with ether (4 × 30 ml) and the organic phase washed with brine, dried (Na_2SO_4), and concentrated to furnish the aldehyde. Purification is accomplished by distillation. The N-methylaminopyridine **3** was recovered in >90% yield by neutralization of the aqueous acidic layer with sodium hydrogen carbonate.

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