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A CONVENIENT METHOD FOR THE PREPARATION OF 6-PHENOXY-2-PYRIDINECARBALDEHYDE[1)]

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6-Phenoxy-2-pyridinecarbaldehyde was prepared in good yields through a few reaction steps utilizing Grignard reaction which has been regarded disadvantageous for preparation of pyridinecarbaldehydes.

6-Phenoxy-2-pyridinecarbaldehyde (2) is a useful intermediate for the preparation of synthetic pyrethroids.[2-4)] As methods for the production of 2, there has been known a few methods in patent literatures, i.e., one is a reduction of methyl 6-phenoxy-2-pyridinecarboxylate with diisobutylaluminium hydride[4)] and another is an oxidation of 2-methyl-6-phenoxypyridine with hydrogen peroxide.[5)]

It has been known that it is difficult to prepare the pyridyl Grignard reagent by direct interaction of a halopyridine with magnesium.[6)] The first successful preparation of a pyridyl Grignard reagent was achieved by submitting 2-bromopyridine to the entrainment method.[7,8)] In the entrainment method, however, it requires an excess amount of another Grignard reagent (ethylmagnesium bromide: ≈3 mol) to complete the reaction effectively and an excess formylating reagent for producing the carbaldehyde. Nevertheless, yields of the carbaldehydes are extremely low at a level of 25 to 50%.[6-9)]

We, however, have found a direct reaction of 2-halo-6-phenoxypyridines (1)[10-12)] with magnesium to form the corresponding Grignard reagent in THF followed by reaction with dimethylformamide to form the desired carbaldehyde (2) of high quality (mp 59.5-61.0 °C) in good yields.

The results are summarized as shown in Table 1, where it can be seen that:

1) even without ethyl bromide (ethylmagnesium bromide)(Run No. 1) which has been considered indispensable to prepare the pyridyl Grignard reagent, the carbaldehyde (2) was obtained in good yield.
2) in the presence of ethyl bromide (Runs No. 2-4) or methyl iodide (Run No. 5), the yields of 2 were increased. The amount of the other Grignard reagents was only 1/10 and less than the amount for the "entrainment method" (≈3 mol).
3) in the case of 2-chloro-6-phenoxypyridine as the starting material (Run No. 7), it was necessary to use ethylmagnesium bromide in amount of 0.7 molar times as much as the amount of the starting material to complete the reaction smoothly and effectively.
4) when ethyl orthoformate was used as formylating agent (Run No. 6), the yield of 2 was lower than the result of Run No. 5 (DMF was used as formylating agent).

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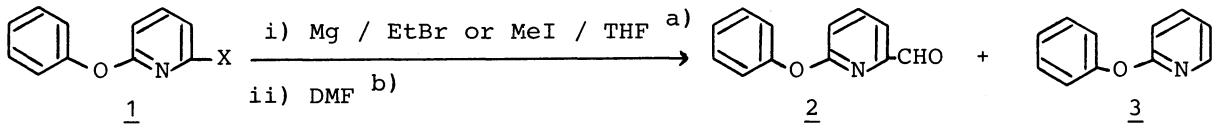
Table 1. Preparation of 6-phenoxy-2-pyridinecarbaldehyde (2) from 2-halo-6-phenoxypyridines (1)



1 2 3

No.	X	1 (mol)	Molar ratio Mg / 1	Molar ratio EtBr or MeI / 1	Products (GLC %) c) 2	3	1
1	Br	0.1	1.2	-	85.7	14.3	-
2	Br	0.1	1.2	0.2	92.0	4.9	-
3	Br	0.1	1.3	0.3	93.6	3.6	-
4	Br	1.0	1.4	0.2	92.1	4.9	-
5	Br	0.01	1.3	0.1(MeI)	87.3	10.4	-
6	Br	0.01	1.3	0.1(MeI) d)	62.4	35.6	-
7	Cl	0.1	2.0	0.7	83.4	5.8	0.9

a) The bromopyridine (1, X = Br) was added dropwise into the Grignard reagent between 40-45 °C for 1.5 h. b) DMF was added dropwise into the cooled reaction mixture (10 °C). Then the mixture was stirred for 3 h at 20 °C and for 0.5 h at 40 °C. c) In Runs No. 2-4 and 7, 2-methyl-3-(6-phenoxy-2-pyridyl)-2-propenal was also produced which would be formed as condensation product of 2 with propanal produced during the reaction. d) Ethyl orthoformate was used as formylating agent.

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