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# REGIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED PYRIDINES VIA GRIGNARD ADDITION TO 1-(ALKOXYCARBOXY)-PYRIDINIUM SALTS

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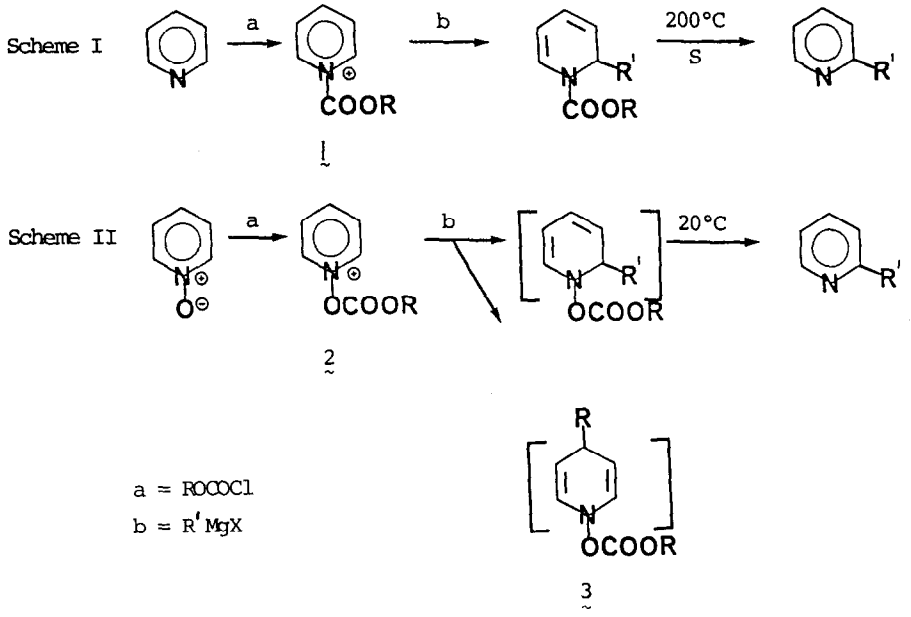
Abstract: A regioselective one pot synthesis of 2-substituted pyridine derivatives from pyridine-1-oxides is described.

A procedure, which has been the method of choice for the synthesis of a number of simple 2-substituted pyridine derivatives, is the addition of Grignard reagents to 1-acylpyridinium salts (1, scheme I)[1,2], followed by the oxidation of the dihydropyridine with elemental sulfur at 200°C.[1] The harsh conditions and relatively poor regioselectivity of this procedure prompted us to consider the alternative route (scheme II). We were surprised to find that this proposed route had not been previously exploited. It is known, however, that when Grignard reagents are allowed to react with pyridine-1-oxide free base, ring opened products can be isolated in good yield.[3] Also, the addition of Grignard reagents to 1-alkoxypyridines is known to give mixtures of 2 and 4 addition products[4], as does the reaction of cyanide with 1-acyloxypyridinium derivatives.[5] Perhaps these negative results have dissuaded others from investigating the route shown in scheme II. We would like to report that this reaction (scheme II) gives moderate yields of 2-substituted pyridines, with very high regioselectivity (>98 percent) under mild conditions.

The synthesis of the unstable 1-alkoxycarboxypyridinium chlorides[6] (e.g. 2) is accomplished by simple addition of ethyl or isobutyl chloroformate to a solution of the pyridine-1-oxide[4] in tetrahydrofuran (THF). The resulting salt precipitates as a white solid. Salts obtained with isobutyl chloroformate appear more stable than those obtained with ethyl chloroformate and therefore are preferred. The salt (2) suspension is treated directly with an aryl, alkenyl or alkynyl Grignard reagent, in the same reaction vessel (alkyl Grignard reagents give complex mixtures). Aqueous work-up, followed by distillation or chromatography, gives the pure products in 41 to 85 percent yield (see Table 1).

In the case of compounds 4 and 5, where authentic standards were available for both the 2- and 4-isomers, a lower limit on the regioselectivity could be established by thin-layer chromatography. In these reactions there was less than 2 percent of the 4-isomer. In all

cases, none of the 4-isomer was ever observed spectroscopically. It seems reasonable to propose that addition to the 4-position of 2 does occur, but this addition product cannot form a favorable cyclic transition state for elimination of alkylcarbonic acid. At this time, however, products such as 3 have not been isolated.

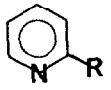
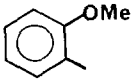
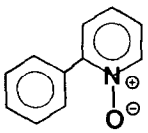
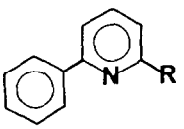
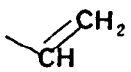
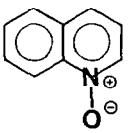
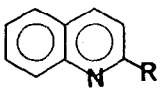



As an example of the typical synthetic procedure, the preparation of 2-phenylpyridine follows: A well-stirred (preferably mechanically) solution of 950 mg of dry pyridine-1-oxide (10 mmole) in 20 ml dry THF at 20°C is treated with 1.3 ml of isobutyl chloroformate (11 mmole), under an atmosphere of argon. The resulting white suspension is cooled in a dry ice/acetone bath (to -50°C) and 6.0 ml of a 2.0 M solution of phenylmagnesium chloride (12 mmole) in THF is rapidly added. Much of the solid goes into solution in ca. 5 min., the mixture is then cooled to -78° for 30 min., and allowed to slowly warm to 20°C. Water (20 ml) is added and the mixture is extracted with ethyl ether (5x75 ml), concentrated and dissolved in 10 ml of 2 M $H_2SO_4$. The acid solution is extracted with $CH_2Cl_2$ (2x75 ml), then neutralized with solid $K_2CO_3$ and extracted with $CH_2Cl_2$ (5x75 ml). The combined organic phase is dried ($K_2CO_3$) and distilled (110°-150°/ca. 1-2 mm) to give 850 mg (55 percent yield) of pure 2-phenylpyridine. The $^1H$ NMR spectrum is identical to the published spectrum.[7]

The examples presented here show that this procedure is useful for the synthesis of a variety of 2 or 2,6-substituted pyridines, from readily available pyridine-1-oxide derivatives. The mild conditions employed make it possible to prepare 2-vinyl or 2-alkynl pyridines, by avoiding the harsh, cumbersome sulfur oxidation that is required by the obvious alternative procedure[1]. The highly regioselective nature of the reaction also greatly facilitates isolation of the pure 2-substituted product, where other procedures give mixtures

of 2 and 4-substituted isomers[1,4]. These combined characteristics make this reaction the procedure of choice for the synthesis of simple alkenyl, alkynyl or aryl pyridine derivatives[15]. The product 5, which has been prepared in multidecagram scale using this procedure, is of interest since it can be transformed into a novel catalytic phosphate protecting group[12]. More work in this area is in progress.

Table 1*

| STARTING MATERIAL | PRODUCT | R | ISOLATED YIELD (%) | COMPOUND # |
|---|---|---|---|---|
|  |  |  | 55**,7,13 | 4 |
| " | " |  | 50**,8,14 | 5 |
| " | " | $-C\equiv C\ SiMe_3$ | 51**,9 | — |
|  |  |  | 43+,7,10 | — |
| " | " |  | 41+,++ | 6 |
|  |  |  | 85+,11 | — |

a) Isobutyl chloroformate/THF
b) RMgX

*All known products are in agreement with published physical and spectroscopic properties.
**Isolated by distillation.
+Isolated by flash chromatography.
++Spectral data for compound 6 (a colorless oil); MS m/e (rel. int.): 181 ($M^+$, 100), 155 (63), 154 (44). $^1H$ NMR δ (TMS, $CDCl_3$): 5.49 (1H, dd, J=10.4, 1.6$H_z$), 6.32 (1H, dd, J=17.6, 1.6$H_z$), 6.91 (1H, dd, J=18.4, 10.4$H_z$), 7.1-7.8 (6H, mult.), 8.05 (2H, mult.).

References

1) D.L. Comins and A.H. Abdullah, J. Org. Chem., 1982, 47, 4315.
2) R. Yamaguchi, Y. Nakazono and M. Kawanisi, Tet. Lett., 1983, 24, 1801.

3) For a comprehensive review of the chemistry of pyridine-1-oxides see R.A. Abramovitch and E.M. Smith, in "Pyridine and its Derivatives", Supplement, ed. R.A. Abramovitch, Wiley, New York, 1974, vol. 2.

4) See O. Cervinka, Coll. Czech. Chem. Commun. 1962, 27, 567.

5) T. Okamoto and H. Tani, Chem. Pharm. Bull., 1959, 7, 925.

6) Compounds of this type are usually unstable, especially in regard to moisture, but in some cases they have been isolated. See Z. Chen and P.J. Stang, Tet. Lett., 1984, 25, 3923, and C.W. Muth and R.J. Dorlak, J. Org. Chem., 1965, 30, 1909.

7) C.J. Ponchert and J.R. Campbell, "The Aldrich Library of NMR Spectra."

8) T.A. Geissman, M.J. Schlatter, I.D. Webb and J.D. Roberts, J. Org. Chem., 1946, 11, 741.

9) T. Sakamoto, M. Shiraiwa, Y. Kondo and H. Yamanaka, Synthesis, 1983, 4, 312.

10) G.R. Newkome and D.L. Fishel, J. Org. Chem., 1972, 37, 1329.

11) Chemical Rubber Company Handbook of Chemistry and Physics, 61st Edition.

12) B.C. Froehler and M.D. Matteucci, J. Am. Chem. Soc., 1985, 107, 278-279.

13) The authors of reference 1 obtained 4 contaminated with 8 percent of 4-phenylpyridine in a combined yield of 60 percent.

14) We have found that the reaction of pyridine, ethyl chloroformate and 2-methoxyphenyl magnesium bromide, followed by sulfur at 200°C (using the optimal procedure of reference 1 for the synthesis of 4) gave a mixture of 5 along with ca. 20 percent ($^1$H NMR) of the 4-substituted isomer, in a combined yield of 50 percent.

15) Though alkyl Grignard reagents do not react cleanly with 1-(alkoxycarboxy)-pyridinium salts, this does not seriously limit the scope of this procedure since 2-alkenylpyridines can be cleanly converted to 2-alkylpyridines in near quantitative yield. For example, 6, 181 mg (1 mmole) and 50 mg of 10 percent Pd on carbon in 5 ml of methanol was stirred under 1 atm. of $H_2$ for 1 h. This mixture was filtered, concentrated and subjected to flash chromatography (3 percent ether/pet. ether) to give 180 mg (98 percent yield) of 2-ethyl-6-phenylpyridine[16].

16) T. Hosokawa, N. Shim, K. Maeda, A. Sonoda and S. Murahashi, Tet. Lett., 1976, 5, 383.

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