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# SYNTHESIS AND SYNTHETIC UTILITY OF 1-ACYL-2-ALKYL-4-TRIMETHYLSTANNYL-1,2-DIHYDROPYRIDINES

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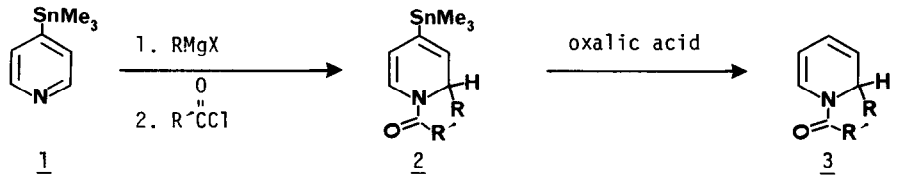
Summary: 1-Acyl-2-alkyl-1,2-dihydropyridines were prepared from 4-trimethylstannylpyridine and Grignard reagents. This methodology was utilized in the synthesis of N-methyl-2-azatricyclo[5.3.1.0]undecane.

The addition of Grignard reagents to 1-acylpyridinium salts affords 1-acyl-2-alkyl-(aryl)1,2-dihydropyridines and 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines. The regioselectivity of this reaction, 1,2- vs. 1,4-addition, is dependent upon the structure of the Grignard reagent[1,2], the 1-acyl group[1], and the presence of cuprous iodide[1,3,4]. The copper-catalyzed Grignard addition to 1-acylpyridinium salts is a convenient method for preparing 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines and 4-alkyl(aryl)pyridines in a regiospecific manner[1,3]. In the absence of cuprous iodide, aryl[1], vinyl[2], and alkynyl[2,5] Grignard reagents give mainly 1,2-addition, whereas most alkyl Grignard reagents give less useful mixtures of 1,2- and 1,4-dihydropyridines. For example, the reaction of ethylmagnesium bromide, pyridine, and ethyl chloroformate gives 1,2- and 1,4-dihydropyridines in a ratio of 64/36[1]. Although some 1-acyl-2-alkyl-1,2-dihydropyridines (e.g., alkyl = Me, Bu) have been prepared by the addition of acyl chlorides and esters to organolithium-pyridine adducts[6], a synthesis of these useful synthetic intermediates[7] from alkyl Grignard reagents is desirable. When the pyridine ring has the 4-position blocked, e.g., 4-picoline, the Grignard reagent adds cleanly to the 2-position of the 1-acyl salt[8]. It occurred to us that if a removable blocking group was at the 4-position during the Grignard reaction, then a regiospecific synthesis of 1-acyl-2-alkyl-1,2-dihydropyridines 3 from alkyl Grignard reagents may be feasible. To this end, we investigated the addition of Grignard reagents to the 1-acyl salts of 4-trimethylstannylpyridine[9] (1). The intermediate 4-trimethylstannyl-




1 2 3

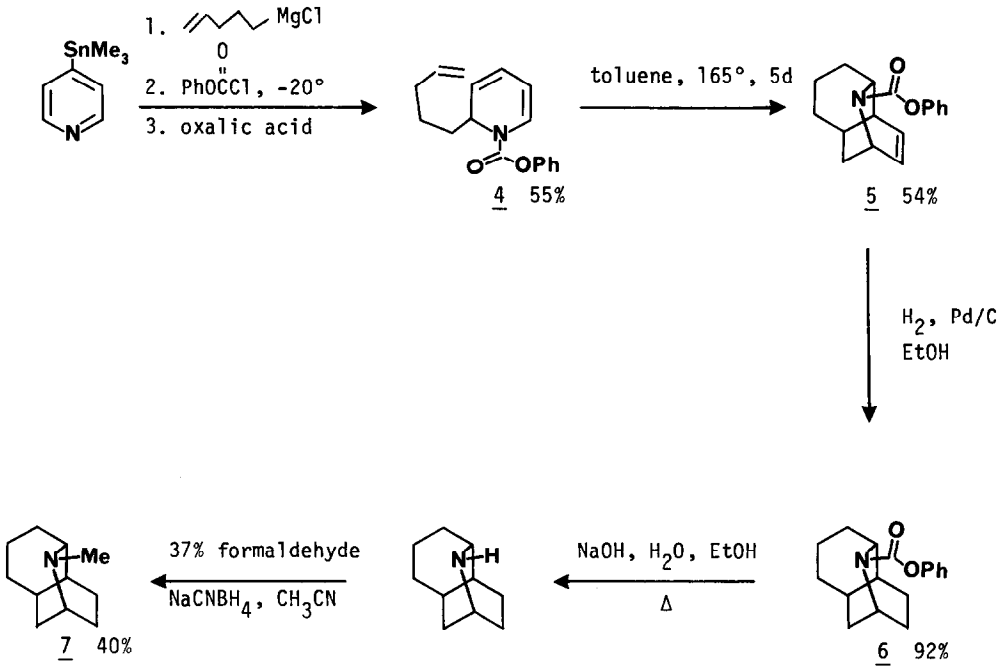
1,2-dihydropyridines 2 could be isolated and purified ($SiO_2$, $CH_2Cl_2$-hexanes; 60-80% yield), or hydrolyzed in situ with oxalic acid to provide 1,2-dihydropyridines 3 via a one-pot reaction (See Table).

TABLE. Synthesis of 1,2-Dihydropyridines 3

| RMgX[a] | acyl chloride | overall yield[b] % | method[c] |
|---|---|---|---|
| n-propylmagnesium chloride | phenyl chloroformate | 68 | A |
| phenylmagnesium chloride | phenyl chloroformate | 70 | A |
| n-butylmagnesium chloride | phenyl chloroformate | 50 | A |
| cyclohexylmagnesium chloride | phenyl chloroformate | 57 | A |
| cyclohexylmagnesium chloride | ethyl chloroformate | 49 | A |
| cyclohexylmagnesium chloride | ethyl chloroformate | 50 | B |
| cyclohexylmagnesium chloride | benzoyl chloride | 39 | B |
| n-butylmagnesium chloride | n-propionyl chloride | 54 | B |
| ethylmagnesium bromide | benzyl chloroformate | 44 | B |
| n-propylmagnesium chloride | ethyl chloroformate | 49 | A |

[a]Reactions were performed on a 2 mmol scale. The acyl chloride (2.0 mmol) was added dropwise to 4-trimethylstannylpyridine (2.2 mmol) and Grignard reagent (2.2 mmol) in THF (-23°C). The mixture was stirred at -23°C for 15 min, then the reaction was worked up using method A or B. [b]Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, $CH_2Cl_2$-hexanes). All products gave the expected IR and $^1H$ NMR spectra. [c]Method A (two-step procedure): The stannyldihydropyridines 2 were isolated (water; $Et_2O$; $MgSO_4$) and treated with oxalic acid (8 mmol), THF (5 ml), and water (1 ml) at RT for 20h to give 3. Method B (one-pot procedure): To the reaction mixture was added water (1 ml) and oxalic acid (8 mmol). After stirring at RT for 20h, extraction with ether provided the crude dihydropyridines 3.

The above methodology was utilized in a short synthesis of N-methyl-2-azatricyclo-[5.3.1.0]undecane (7) ("dihydrocannivonine")[10]. Dihydropyridine 4 was prepared from 4-trimethylstannylpyridine[9] in 55% yield using a one-pot procedure. The triene 4 in toluene was heated at 165 °C under argon for 5 days to give the tricyclic carbamate 5 (54%)[11]. Catalytic hydrogenation gave 6, which was hydrolyzed and N-methylated[12] to give N-methyl-2-azatricyclo[5.3.1.0]undecane (7). A synthesis of 7 has previously been accomplished by Evans and coworkers[13]. Our spectral data[14] for 7 ($^1$H NMR, $^{13}$C NMR, and IR) were in agreement with their reported[13] spectral data for this compound (7).

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References and Notes.

1. D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, 47, 4315.
2. R. Yamaguchi, Y. Nakazono, and M. Kawanisi, Tetrahedron Lett., 1983, 24, 1801.
3. D. L. Comins, Tetrahedron Lett., 1983, 24, 2807; D. L. Comins and N. B. Mantlo, ibid., 1983, 24, 3683; D. L. Comins and N. B. Mantlo, J. Heterocycl. Chem., 1983, 20, 1239; D. L. Comins, E. D. Stroud, and J. J. Herrick, Heterocycles, 1984, 22, 151; D. L. Comins, R. K. Smith, and E. D. Stroud, ibid., 1984, 22, 339.
4. Stoichiometric organocopper reagents (e.g., $R_2CuLi$, RCu, $RCu{\cdot}BF_3$) also preferentially attack the 4-position of 1-acylpyridinium salts. E. Piers and M. Soucy, Can. J. Chem., 1974, 52, 3563; K. Akiba, Y. Iseki, and M. Wada, Tetrahedron Lett., 1982, 23, 429.
5. Silver phenylacetylide also preferentially attacks the $\alpha$-position of 1-acylpyridinium salts. T. Agawa and S. I. Miller, J. Am. Chem. Soc., 1960, 83, 449.
6. C. S. Giam and E. E. Knaus, Tetrahedron Lett., 1971, 4961; C. S. Giam, E. E. Knaus, and F. M. Pasutto, J. Org. Chem., 1974, 39, 3565.
7. For a recent review on dihydropyridines, see D. M. Stout and A. I. Meyers, Chem. Rev., 1982, 82, 223.
8. G. Fraenkel, J. W. Cooper, and C. M. Fink, Angew. Chem., Int. Ed. Engl., 1970, 9, 523; R. E. Lyle, J. L. Marshall, and D. L. Comins, Tetrahedron Lett., 1977, 1015; R. E. Lyle and D. L. Comins, J. Org. Chem., 1976, 41, 3250.
9. Y. Yamamoto and A. Yanagi, Chem. Pharm. Bull., 1982, 30, 1731.
10. Structure 7 was incorrectly assigned to a derivative of a natural product, "cannivonine", isolated from cranberry leaves. K. Jankowski, Tetrahedron Lett., 1976, 3309. For an unambiquous total synthesis of 7, see ref. 13.
11. For a similar intramolecular Diels-Alder reaction, see D. L. Comins, A. H. Abdullah, and R. K. Smith, Tetrahedron Lett., 1983, 24, 2711.
12. R. F. Borch and A. I. Hassid, J. Org. Chem., 1972, 37, 1673.
13. D. A. Evans, A. M. Golob, N. S. Mandel, and G. S. Mandel, J. Am. Chem. Soc., 1978, 100, 8170.
14. Compound 7: $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$2.85-2.3 (m, 2H), 2.4 (s, 3H), and 2.2-1.1 (broad m, 14H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 60.5, 50.4, 42.6, 33.5, 32.0, 30.6, 29.8, 29.3, 25.7, 18.3, and 15.9; IR (neat) 2930 $cm^{-1}$; GC/MS, $M^+$ 165.

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