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INTRODUCTION OF FUNCTIONAL GROUPS INTO 6 POSITION OF PYRIDOXAL

Yasuhiro Yamada*, Toshio Hayashi, Yuichi Fusho and Hirosuke Okada
Department of Fermentation Technology, Faculty of Engineering,
Osaka University, Yamadakami, Suita-shi, Osaka, Japan

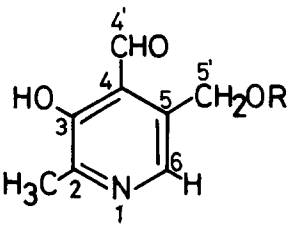
Summary: The synthesis of 6-acylpyridoxal, 6-carboxyethylpyridoxal and 6-(3'-aminopropyl)pyridoxal derivatives are described.

Pyridoxal-5'-phosphate (2), the active form of vitamin B_6, is a coenzyme of many enzymes which catalyze transamination, decarboxylation, deamination, β-elimination and β-substitution of amino acids.

Pyridoxal (1), (2) and their derivatives also show some physiological activities.[1)] These facts have stimulated studies on the relation of their structure and activities. Although many derivatives of V.B_6 were reported, of which greater part were modified in position other than 6 position of their pyridine ring and only a few of them have a substituent on 6 position.[1b, 2)] In order to obtain variants of pyridoxal or pyridoxal-5'-phosphate which retain their coenzyme activities and are applicable to immobilized coenzymes, the introduction of carbon functional groups into open 6 position of pyridoxal and elongation of them to appropriate spacers is a promising method.

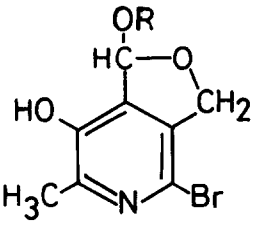
In this communication, we wish to describe an acylation of 6 position of appropriately protected pyridoxal via its lithium compound and preparation of some 6-substituted pyridoxal derivatives.

Bromination of pyridoxal with pyridinium hydrobromide perbromide in $CHCl_3$ at room temperature with vigorous stirring for 3 h gave 6-bromopyridoxal (3) in 57% yield, [mp 138° (dp); mass, 247, 245 (M^+); NMR (in d-DMSO) δ, 2.40 (CH_3), 4.85 (5'-CH_2-,d), 6.50 (4'-CH-); UV (in MeOH) nm, 225 (9,500), 288 (6,600)]. (3) was transformed to 6-bromo methylacetal (4) (mp 149°) by HCl in dry methanol



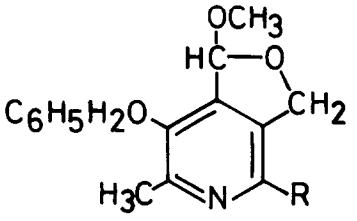
(1) R=H

(2) $R=PO_3H_2$



(3) R=H

(4) $R=CH_3$



(5) R=Br

(6) R=Li

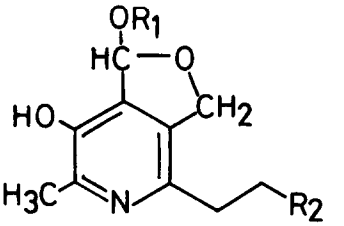
(7) R=CHO

(8) $R=COCH_3$

(9) $R=CO(CH_2CH_2O)_3CH_2C_6H_5$

(10) R=CH=CHCOOH

(11) R=CH=CHCN



(12) $R_1=CH_3$, $R_2=COOH$

(13) $R_1=H$, $R_2=COOH$

(14) $R_1=CH_3$, $R_2=CH_2NH_2$

in 92% yield. (4) was benzylated with dimethylphenylbenzylammonium chloride[3] in ethanol in the presence of sodium ethoxide to give 6-bromo-3-O-benzyl methylacetal (5) in 82% yield, [mp 110°; NMR (in $CDCl_3$) δ, 2.46 (CH_3), 3.45 (OCH_3), 4.95 (5'-CH_2-,d), 5.10 (Ar-CH_2-), 6.18 (4'-CH-), 7.33 (Ar-H); UV (in MeOH) nm, 225 (sh), 285 (6,770)].

Bromine atom in (5) was substituted with lithium by treating (5) with n-butyllithium in THF at -78° under argon. To the lithium compound (6) colored

dark red, was added 1.5 equiv. dimethylformamide in dry THF and kept for 4 h. After treating reaction mixture with dil. HCl, usual workup gave 6-formyl-3-O-benzyl methylacetal (7) in 72% yield,[4] [mp 103°; mass, 299 (M^+), 268; NMR (in $CDCl_3$) δ, 2.60 (CH_3), 3.49 (OCH_3), 6.25, 5.60 (4'-CH_2-, d, J=12 Hz), 5.34 ($ArCH_2O$), 6.30 (4'-CH-), 7.40 (Ar-H), 10.0 (-CH=O), UV (in MeOH) nm, 293 nm (9,620), 275 (sh)].

Reaction of lithium compound (6) with N,N-dimethylacetamide and N,N-dimethyl-4,7,10-trioxa-11-phenylundecanoyl-1-amide gave corresponding 6-acylpyridoxal derivatives (8) and (9) in 18 and 6% yields respectively. (8) [mp 95°; mass, 322 (M^+); NMR (in $CDCl_3$) δ, 2.56, 2.66 (-CH_3), 3.45 (-OCH_3), 3.2-3.5 (5'-CH_2-, Ar-CH_2-), 6.26 (4'-CH-), 7.39 (Ar-H), UV (in EtOH) nm, 294 (11,200), 260 (8,320)]. (9) [oil; mass, 521 (M^+); NMR (in $CDCl_3$) δ, 2.48 (-CH_3), 3.42 (OCH_3), 3.88 (-CO-CH_2-$\underline{CH_2}$-O-, t, J=6), 5.28 ($ArCH_2$-O-3-C), 5.18, 5.42 (5'-CH_2-, d, J=12 Hz)].

In both cases, debrominated 6-H compound was obtained as a main product. Low yields of these products (8) and (9) were probably due to the release of α-methylene proton of amids which reacted with (6) to give 6-H compound.

All attempts to alkylate lithium compound (6) with alkylhalides such as allylbromide, allyliodide and other alkylating reagents were unseccessful. This fact is interesting considering that Rapoport *et al.*[5] successfully alkylated α-lithiumpyridine compound with several prenylbromides in their synthesis of piericidin analogues.

6-Formylpyridoxal derivative (7) is an useful intermediate for the synthesis of 6-alkylpyridoxal derivatives. For example, we have synthesized 6-carboxyethylpydoxal (13) and 6-(3'-aminopropyl)pyridoxal derivative (15) from (7). (7) was condensed with malonic acid in pyridine in the presence of a trace amount of piperidine at 80° for 2 h to give 6-carboxyvinyl-3-O-benzyl methylacetal (10) in 79.5% yield, [mp 192°; mass, 341 (M^+), 310, 219; NMR (in d-DMSO) δ, 2.42 (CH_3), 3.38 (OCH_3), 5.1-5.3 ($ArCH_2$,5'-CH_2-), 6.44 (4'-CH-), 6.60 (=CH-CO, d, J=16 Hz), 7.24-7.5 (-CH=, Ar-H); UV (in MeOH) nm, 285 (6,920)]. Similarly 6-cyanovinyl-3-O-benzyl methylacetal (11) was obtained by condensation of (7) with cyanoacetic acid in 65% yield. [mp 125°; IR (Nujol) 2,200 cm^{-1} (C≡N), NMR (in $CDCl_3$) δ, 2.52 (CH_3), 3.46 (OCH_3), 5.1-5.5 ($ArCH_2$-, 5'-CH_2-), 6.24 (4'-CH-), 6.40 (=CH-CN, J=16 Hz), 7.15 (-CH=, J=16 Hz), 7.39 (Ar-H); UV (in EtOH) nm, 320 (20,900), 272 (13,000), 223 (sh)].

(10) was hydrogenated over Pd-C (5%) in MeOH-THF (2:1) at room temperature under an atmospheric pressure for 3 h to give (12) in 56% yield in a pure crystalline form. [mp (dp) 170-180°; mass, 221 (-CH_3OH), 176; NMR (in d-DMSO) δ, 2.36 (CH_3), 2.5-2.8 (-CH_2CH_2-CO), 3.30 (OCH_3), 4.96 (5'-CH_2-), 6.16 (4'-CH-), UV (in MeOH) nm, 285 (6,920)].

(12) was easily hydrolyzed to (13) with 1 N HCl at 50° for 1 h quantita-

tively.

The unsaturated nitrile (11) was also hydrogenated to saturated amine (14) over Pd-C (15%) in ethanol in the presence of small amount of $CHCl_3$[6] under 1 atm of H_2 at room temperature. This amine (14) was purified and identified in the form of diacetate in 52% yield, [oil, NMR (in $CDCl_3$) δ, 1.94, 2.34, 2.42 (CH_3), 1.75-2.15 (C-CH_2-C), 2.71 (6C-CH_2-, t), 3.2-3.5 (-CH_2-N), 5.10 (5'-CH_2-, d, d), 6.12 (4'-CH-), 6.40 (NH)].

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