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A NEW METHOD FOR REGIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED 1-(METHOXYCARBONYL)-1,2-DIHYDROPYRIDINES[1]

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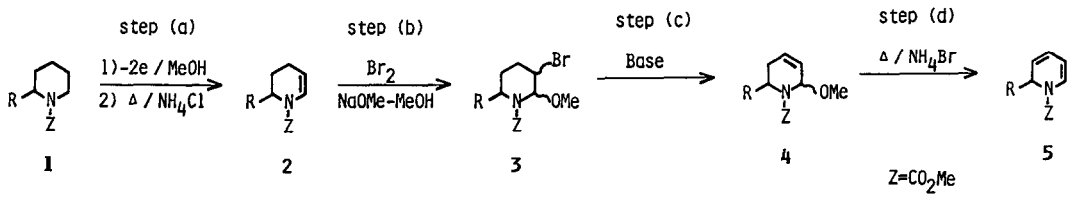
Summary: 2-Substituted 1,2-dihydropyridines including an optically active one were regioselectively prepared from 2-substituted piperidines through three intermediates, that is, (a) 1,2,3,4-tetrahydropyridines, (b) 5-bromo-6-methoxypiperidines, and (c) 1,2,3,6-tetrahydro-6-methoxypyridines.

Since 1-acyl-1,2-dihydropyridines have been known to be useful synthetic intermediates as exemplified by their Diels-Alder type reaction to form nitrogen-heterocycles,[2] a variety of methods have been reported for synthesis of these dienes.[3] Although the reported syntheses known to be useful ones have been carried out by reduction of pyridinium salts[4] or by addition of organometallic reagents to pyridinium salts,[5] these methods form both 1,2- and 1,4-dihydropyridines. Thus, convenient methods for the selective synthesis of 1,2-dihydropyridines, especially those possessing substituents at certain positions of pyridine nucleus are quite few so far.[6] We report herein a new facile method for the regioselective synthesis of 2-substituted 1-(methoxycarbonyl)-1,2-dihydropyridines 5 from piperidines 1.

Scheme 1 shows our method which comprises (a) preparation of tetrahydropyridines 2 from 1, (b) bromomethoxylation of 2, (c) dehydrobromination of 3 to tetrahydromethoxypyridines 4, and (d) elimination of methanol from 4 affording 5.



Scheme 1

The selective preparation of 2a-d was achieved according to our previously reported method.[7] The addition of Br_2 (1.1 eq.) to a solution of 2a-d in methanol containing NaOMe (1.1 eq.) at rt gave 3a-d, which was then dehydrobrominated by treatment with bases[8] (DBU in DMF at 90°C or electrochemically generated 2-pyrrolidone anion[9] in DMF at rt) to afford 4a-d. The desired 5a-d were obtained by heating (90-100°C) 4 in the presence of NH_4Br (0.01 eq.) under reduced pressure (70-100 mmHg) for 1-2 h.[7] The yields of 2-5 are summarized in Table 1. The compounds 4 as well as 5 were found to give the Diels-Alder type adducts upon reaction with dienophiles under acidic conditions. For example, the reaction of 4c with dimethyl fumarate in toluene containing a catalytic amount of *p*-TsOH at 100°C gave [4+2] cycloadduct

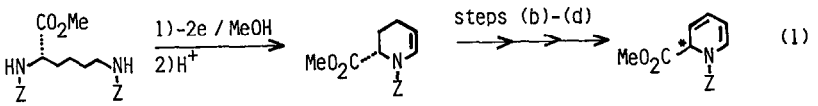
Table 1. Isolated Yields (%) of Compounds 2-5

	R	2	3	4	5
a	H	83	80	72[a] (77)[b]	65
b	Me	64	80	50[a]	65
c	Et	74	84	74[a]	89
d	CH_2COMe	60	56	78[a]	85

[a,b] Used base: [a] DBU (2 eq.). [b] Electrochemically generated 2-pyrrolidone anion (2 eq.).

in 52% yield.

Furthermore, our method was applied to the synthesis of 5e which was the first example of optically active 1,2-dihydropyridine. The key intermediate 2e for the preparation of 5e was preparable (ca. 100% ee) by our reported method starting from L-lysine derivative 6 (eq. 1).[10] The optical purity of 5e ($[\alpha]_D^{25}$ -516.7° (c 1.2, MeOH)) obtained according to the procedures shown above (step b, 72%; step c, 80%; step d, 80%) was found to be at least 77% ee after it was converted to 1e (R = CO_2Me) by hydrogenation (1e; $[\alpha]_D^{25}$ -47.0° (c 1.5, MeOH), an authentic sample; $[\alpha]_D^{25}$ -60.9° (c 1.5, MeOH)).



6 2e Z=CO_2Me 5e

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