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SYNTHESIS OF N-LAUROYLVALINE DERIVATIVES

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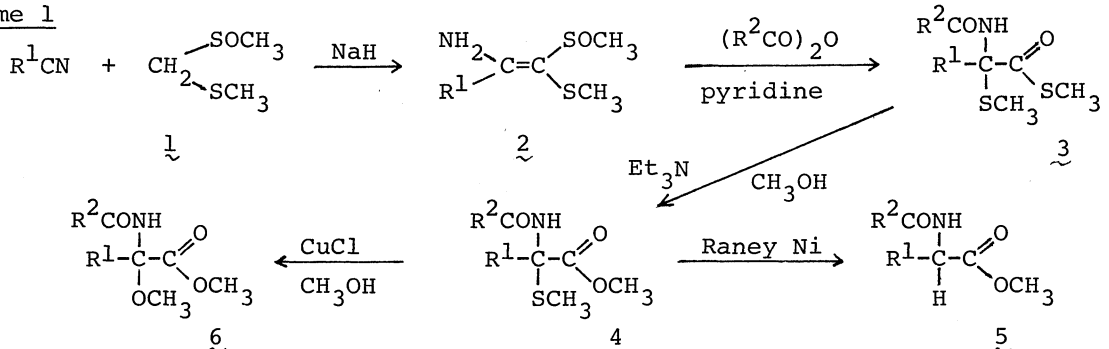
Methyl ester of N-lauroylvaline, as well as its α-methylthio and α-methoxy derivatives, was synthesized, starting from 1-methylsulfinyl-1-methylthio-2-amino-3-methyl-1-butene (2, R^1 = i-Pr) which was obtained by the reaction of isobutyronitrile and methyl methylthiomethyl sulfoxide (1).

It is known that some of N-acylamino acids have notable antibacterial activity.[1] Among them, N-lauroylvaline shows the most constant activity on rice blast disease, and it is hopeful to use this compound as one of agricultural chemicals, which may not bring about enviromnental pollution.[2] Now, we wish to communicate on the synthesis of methyl ester of N-lauroylvaline, as well as its α-methylthio and α-methoxy derivatives as shown in Scheme 1.

Scheme 1



a R^1 = i-Pr R^2 = $CH_3(CH_2)_{10}$; b R^1 = R^2 = CH_3;
c R^1 = i-Pr R^2 = CH_3; d R^1 = Ph R^2 = CH_3

Methanethiol ester (3a) of N-lauroyl-α-methylthiovaline, a key intermediate for the preparation of N-lauroylvaline derivatives, was obtained by the reaction of lauric anhydride with 2 (R^1 = i-Pr).[3] A solution containing 970 mg of 2 (R^1 = i-Pr), 2.83 g of lauric anhydride, and 0.6 ml of pyridine in 15 ml of methylene chloride was stirred at room temperature for 18 hr. After the removal of methylene chloride and pyridine under reduced pressure, the residue was column-chromatographed on silica gel to give 1.28 g (68%) of 3a (mp 58-59°C),[4] along with 43 mg of the recovered 2 (R^1 = i-Pr). We further examined the transformation reaction of 2 (R^1 = i-Pr) into 3a by using other activated derivatives of lauric acid: Lauroyl chloride (-70-0°C, 1 hr) and lauric methoxycarboxylic anhydride (room temperature, 65 hr) reacted with 2 (R^1 = i-Pr) to give 3a in 33% and 49% yields, respectively, but p-nitrophenyl laurate did not give any satisfactory

result.

The methanethiol ester (3a) thus obtained was quantitatively converted into the corresponding methyl ester (4a) by stirring in methanol containing a small amount of triethylamine at 40°C for 18 hr, and 4a was reduced with Raney Ni (WII activity) in ethanol to give N-lauroylvaline methyl ester (5a, mp 52-53°C) in 89% yield.[5] Interestingly, the replacement of the α-methylthio group in 4a by methoxy group was achieved by treating with cuprous chloride in methanol at room temperature (about 1 day), affording N-lauroyl-α-methoxyvaline methyl ester (6a, mp 59-60°C) in 93% yield.[6] This replacement reaction could also be applied to other N-acetyl-α-methylthioamino acids (4b, 4c, and 4d) and, in a similar manner, N-acetyl-α-methoxyamino acids (6b, 6c, and 6d) were obtained in 79%, 97%, and 92% yields, respectively.[10]

Further application of the present method to the syntheses of other N-acylamino acids and their α-methoxy derivatives is being studied. The examination for antibacterial activities of 4a and 6a is also in progress.

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3. K. Ogura and G. Tsuchihashi, J. Amer. Chem. Soc., 96, 1960 (1974).
4. Satisfactory elemental analyses have been obtained for all new compounds reported herein, along with sufficient physical data (IR and NMR spectra) to determine the structures.
5. The conversion of 4a into 5a can also be effected by sodium borohydride in pyridine at room temperature.
6. Although C-6(7) methylthiopenicillin and cephalosporin derivatives can be converted into the corresponding C-6(7) methoxypenicillin and cephalosporin derivatives on treatment with silver nitrate,[7] mercuric salts,[8] or tallium trinitrate[9] in methanol, the effect of cuprous chloride on these replacement reactions is hitherto unknown.
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