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Note

Synthesis of [$^{13}C_2$]nifedipine

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Summary

[$^{13}C_2$]Nifedipine (3) was synthesized from [^{13}C]methanol (1) in two steps.

Key Words: Hantzch reaction; [$^{13}C_2$]nifedipine; di[^{13}C]methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate; [^{13}C]methyl 3-oxobutanoate; [^{13}C]methanol

Introduction

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (3) (Bayer 1040; Nifedipine), a calcium channel blocker used clinically in the treatment of hypertension and oxygen deficiency diseases of the heart,[1] is synthesized by application of the Hantzch reaction.[2] Since the ^{13}C-labeled drug would be useful in ^{13}C-NMR studies of its interactions with other drugs or biological molecules, we synthesized ^{13}C-labeled nifedipine (3).

Results and discussion

As shown in Scheme 1, [^{13}C]methanol (1) was esterified with diketene in the presence of a catalytic amount of dry triethylamine to afford

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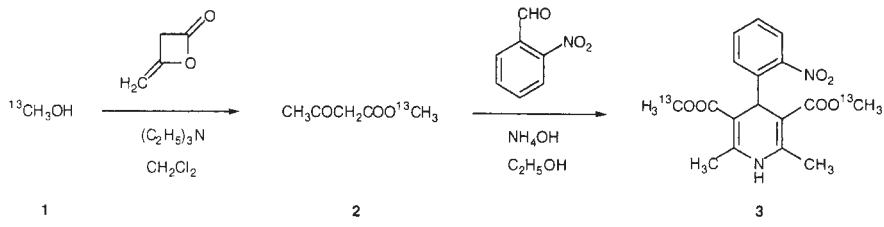

1 2 3

Scheme 1.

[^{13}C]methyl 3-oxobutanoate (2).[3] Reaction of this product (2) with 2-nitrobenzaldehyde, and ammonia solution (28%) gave [$^{13}C_2$]nifedipine (3) in 85% yield.

Experimental

Materials

[^{13}C]Methanol (99.5 atom% ^{13}C) was purchased from Isotec Inc. All other chemicals were of analytical grade.

Instruments

Melting point determinations were carried on a Yanaco micro-melting point apparatus, Model MP; values are uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.4 MHz) spectra were recorded on a Varian Gemini 2000 spectrometer. EI-MS spectra were obtained on a JMS-700 spectrometer.

[^{13}C]Methyl 3-oxobutanoate (2)

Dry triethylamine (0.3 ml, 2.2 mmol) followed by diketene (2.5 ml, 32.7 mmol) was added to [^{13}C]methanol (1) (0.87 ml, 21.4 mmol) in dry dichloromethane (20 ml). The mixture was refluxed for 2 h, then allowed to cool to room temperature, and water was added. The solution was extracted with ether three times and the combined extracts were washed with brine, then dried ($MgSO_4$) and evaporated. Distillation of the crude product gave [^{13}C]methyl 3-oxobutanoate (2) (2.52 g, quant.), b.p. 65–73°C (28 mmHg); ^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3 H), 3.49 (d, 3 H, $J = 9.6$ Hz), 4.00 (s, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 52.4; EI-MS m/z (rel. int. %): 117 (M^+, 29).

Di[^{13}C]methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (3)

A solution of [^{13}C]methyl 3-oxobutanoate (2) (0.93 ml, 8.6 mmol), ammonia solution (28%) (0.6 ml, 10 mmol) and 2-nitrobenzaldehyde (0.65 g, 4.3 mmol) in dry ethanol (5 ml) was refluxed for 3 h, then the mixture was evaporated. The residue was recrystallized from ethanol-ether to give di[^{13}C]methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (3) (1.26 g, 85%), m.p. 169–173°C; ^{1}H-NMR ($CDCl_3$) δ: 2.49 (s, 6 H), 3.59 (d, 6 H, $J = 144.7$ Hz), 5.72 (s, 1 H), 7.20 (m, total 4 H); ^{13}C-NMR ($CDCl_3$) δ: 51.0; EI-MS m/z (rel. int. %): 348 (M^+, 10).

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