

RESEARCH ARTICLE

Synthesis of ^{15}N -labelled 3,5-dimethylpyridine

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Funding information

European Human Capital & Mobility Network "Localization and Transfer of Hydrogen", Grant/Award Number: ERBCHRXCT949582

^{15}N -labelled pyridines are liquid- and solid-state nuclear magnetic resonance (NMR) probes for chemical and biological environments because their ^{15}N chemical shifts are sensitive to hydrogen-bond and protonation states. By variation of the type and number of substituents, different target pyridines can be synthesized exhibiting different pK_a values and molecular volumes. Various synthetic routes have been described in the literature, starting from different precursors or modification of other ^{15}N -labelled pyridines. In this work, we have explored the synthesis of ^{15}N ^{15}N -labelled pyridines using a two-step process via the synthesis of alkoxy-3,4-dihydro-2*H*-pyran as precursor exhibiting already the desired pyridine substitution pattern. As an example, we have synthesized 3,5-dimethylpyridine- ^{15}N (lutidine- ^{15}N) as demonstrated by ^{15}N -NMR spectroscopy. That synthesis starts from methacrolein, propenyl ether, and ^{15}N -labelled NH_4Cl as nitrogen source.

KEYWORDSisotope labelling, lutidine, nitrogen-15, pyridine, 2*H*-pyran, nitrogen-15, isotope labelling, synthesis, 2*H*-pyran

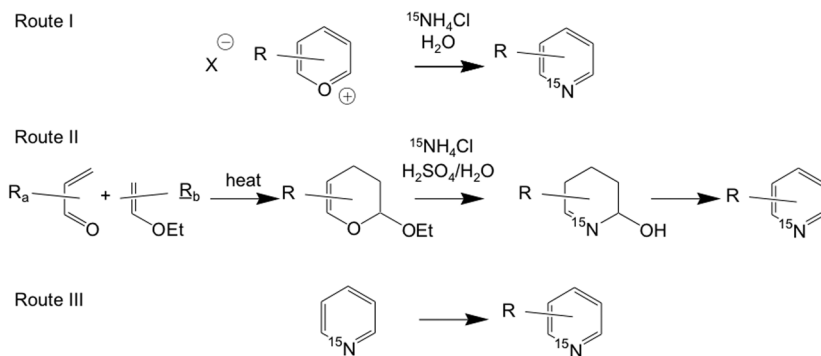
1 | INTRODUCTION

^{15}N -labelled pyridines and related heterocycles are important liquid- and solid-state nuclear magnetic resonance (NMR) probes for chemical and biological environments.^{1–6} That feature arises on one hand from the basicity of pyridines and their ability to form hydrogen bonds. On the other hand, ^{15}N chemical shifts are very sensitive to the ^{15}N - ^1H distance and can be used to monitor the local H-bond and protonation state.^{7–9} Therefore, ^{15}N -labelled pyridines have been used to explore the acidity of mesoporous surfaces or of biological environments using high-resolution solid-state NMR spectroscopy. Moreover, the mobility of pyridines to jump from one proton donor to another allows one to obtain interesting information about local structures.²

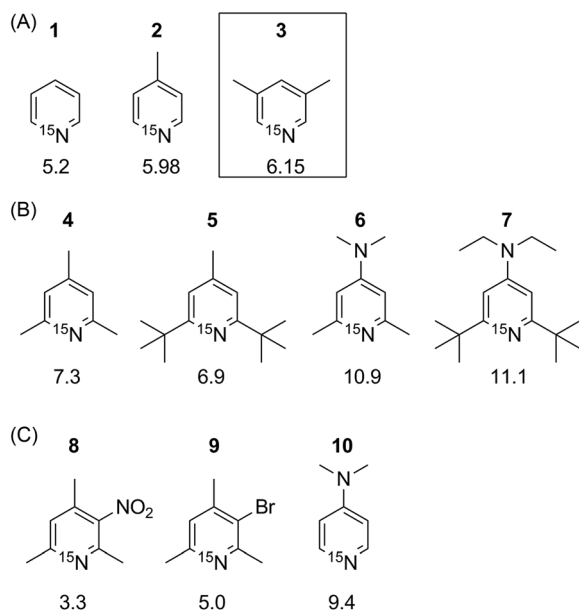
So far, ^{15}N pyridine is the only representative that is commercially available in a ^{15}N -labelled form. Thus, syntheses of various ^{15}N -labelled pyridine derivatives with a large range of pK_a values have been reported so far, applying several routes as illustrated in Scheme 1. Route I starts from the appropriate pyrylium salt containing already the desired pyridine substituents, using $^{15}\text{NH}_4\text{Cl}$ as nitrogen source. In Route II, alkoxy-3,4-dihydro-2*H*-pyrans exhibiting the desired substituents are firstly synthesized as precursors via a Diels-Alder addition of vinyl ethers to α,β -unsaturated carbonyl compounds. The pyrans can then easily be converted into the corresponding ^{15}N -labelled pyridines using $^{15}\text{NH}_4\text{Cl}$. Finally, easily available labelled pyridines can be converted into other derivatives (Route III). Some examples are depicted in Scheme 2.

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SCHEME 1 Synthetic routes to ^{15}N -labelled pyridine derivatives



SCHEME 2 Overview of the so-far reported ^{15}N -labelled pyridine derivatives obtained either by Route II (A), Route I (B), or Route III (C)

Up to date, most ^{15}N -labelled pyridines have been synthesized following Route I, namely, 2,4,6-trimethyl-pyridine **4**, also called collidine,¹⁰ 2,6-di-tert-butyl-4-methyl-pyridine **5**,¹¹ 4-dimethylamino-2,6-dimethyl-pyridine **6**,¹² and 4-diethylamino-2,6-di-tert-butyl-pyridine **7**.¹¹ However, Route I is limited to pyridines with aliphatic substitutions at C2 and C6. Route II has been used to synthesize ^{15}N -labelled plain pyridine **1**^{12,13} and 4-methyl-pyridine **2**.⁹ Route III was used for the synthesis of ^{15}N -labelled 2,4,6-trimethyl-3-nitro-pyridine **8**, 2,4,6-trimethyl-3-bromo-pyridine **9** and 4-N,N-dimethylamino-pyridine **10**.¹²

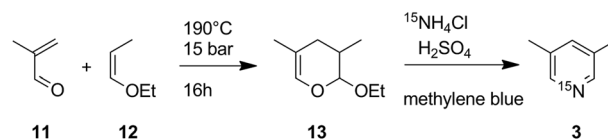
As we wanted to obtain 3,5-dimethyl-pyridine- ^{15}N (**3**) as molecular sensor for comparison with pyridine- ^{15}N (**1**) and collidine- ^{15}N (**4**), we explored the most suitable route to synthesize **3**. We could not use Route I as pyrylium salts without substituents in 2- and 6- position are rare and not very stable.¹⁴ In addition, it is not possible to obtain **3** from **1** via Route III. Therefore, we

checked in more detail Route II. That route had been used to synthesize pyridine- ^{15}N (**1**). The required precursor 3,4-dihydro-2-methoxy-2*H*-pyran is commercially available and can be synthesized in solution at high pressures up to 15 000 bar¹⁵ or under milder conditions using either dry-state adsorption conditions¹⁶ or an ytterbium catalyst.¹⁷ The original synthesis of Longley and Emerson¹⁸ did not use a solvent or additives but only the neat reactants, heating them up to about 200 °C in a normal laboratory autoclave. The pressure achieved was not reported, but they probably did not exceed about 15 bar.¹⁸ Therefore, that method seemed to us preferable as only small quantities of the pyran are needed. We found that this method was suitable and succeeded to synthesize in a similar way also 4-methyl-pyridine- ^{15}N (**2**).⁹ Therefore, we want to describe here in more detail how to prepare pyridines for which commercial precursors are not available, using the example of ^{15}N -labelled 3,5-dimethylpyridine (**3**).

2 | RESULTS AND DISCUSSION

In the first stage of this work, we checked out alternative routes starting from unlabelled 3,5-dimethyl pyridine, but these efforts were not successful.

As precursor of the Diels-Alder reaction, we used methacrolein **11** and ethyl 1-propenyl ether **12** leading to 2-ethoxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran **13** (Scheme 3). Methacrolein was stabilized with a small amount of hydroquinone to avoid polymerization. Nuclear magnetic resonance spectroscopy revealed a *cis/trans* mixture of compound **13** in the ratio of 2:3 (Figure 1); the



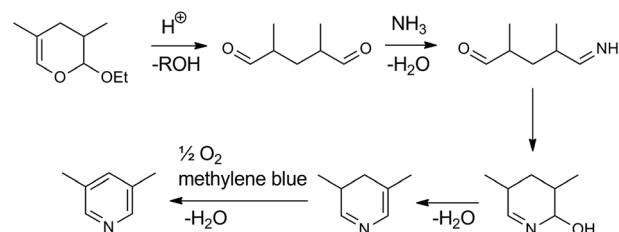
SCHEME 3 Synthetic route to ^{15}N -labelled lutidine used in this work

chemical shifts are listed and compared to literature values in Table 1. The chemical shifts and coupling constants of the two 2*H*-pyran ring isomers fit very well to previous reports for 2-benzoyloxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran from Yamamoto et al.¹⁹ and 2-methoxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran from Descotes et al.²⁰ Although the diastereomers could potentially be separated by chromatography, a separation was not required because both diastereomers are an in situ source of 1,5-pentane-dial that is generated in the initial part of the second step of the synthesis. A side product of the reaction was the Diels-Alder reaction of methacrolein with itself forming 3,4-dihydro-2*H*-pyran-2-carbaldehyde, which was however reduced by using an excess of the dienophile and was separated by distillation.

In the second step, the dihydropyran mixture was converted to 3,5-dimethylpyridine according to Scheme 4. ¹⁵N-labelled 3,5-dimethylpyridine was isolated as an aqueous azeotrope by steam distillation of the basified reaction mixture, after volatile substances were initially removed by distillation of the acidic reaction mixture. Methylene chloride was used to extract the product from the azeotrope with yields of ~ 55% relative to the amount of the ¹⁵N isotope used.

2.1 | NMR characterization of 3,5-dimethylpyridine

The ¹H NMR spectrum of ¹⁵N-labelled 3,5-dimethylpyridine was identical to the unlabelled



SCHEME 4 Proposed mechanism of the formation of 3,5-dimethylpyridine in analogy to Whaley and Ott¹³

compound, except that the protons adjacent to the ¹⁵N nucleus show a splitting of 10.6 Hz due to the ²J_{HN} scalar coupling. The coupling is in agreement with previous reports measured in the same solvent.²¹ The observed ¹H and ¹³C resonances agree with previously reported values measured in the same solvent,²² except that we assigned the ¹³C signal at 137.0 ppm to C3/C5 and 132.4 ppm to C4 (swapped in Pazderski et al). Our ¹³C assignment agrees also with the data measured in DMSO-*d*₆ and D₂O despite small deviations due to the different solvents.^{23,24} Although the ¹³C spectrum of labelled and unlabelled 3,5-dimethylpyridine looked virtually identical, a closer interpretation revealed a small splitting of two signals due to small ¹J_{CN} scalar couplings. Interestingly, no splitting was observed for the two carbons directly adjacent to the nitrogen nucleus, but the signals of C₃, C₅, and C₄ showed a splitting. Values of 3.1 Hz for ²J_{CN} and of 3.5 Hz for ³J_{CN} were observed, which are in a similar range as those observed in ¹⁵N-labelled pyridine (²J_{CN} = -2.53 Hz and ³J_{CN} = -3.85 Hz²⁵). ¹J_{CN} was too small to be detectable in a splitting in agreement

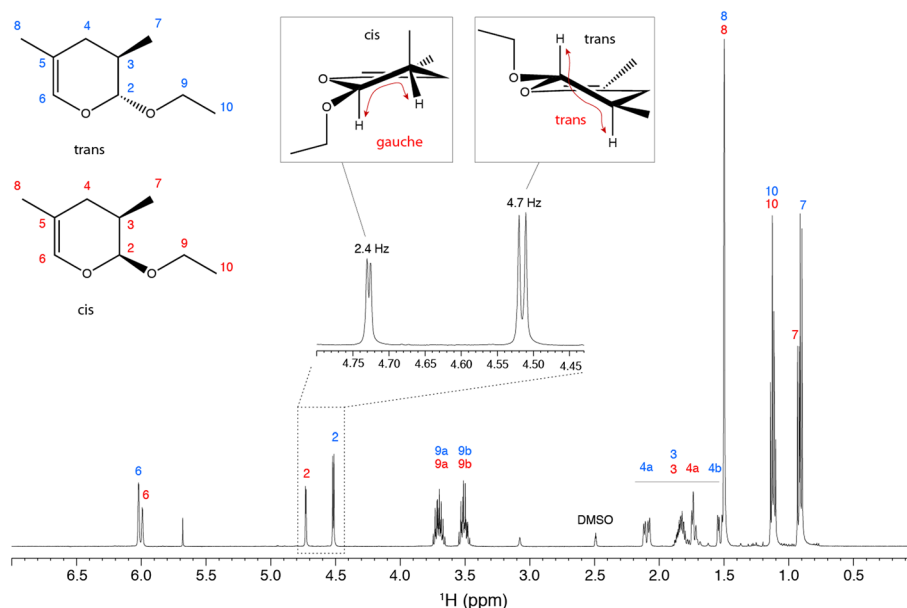


FIGURE 1 ¹H NMR spectrum of 2-ethoxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran **13** consisting of a 2:3 *cis/trans* mixture measured in DMSO-*d*₆. For clarity, only one enantiomer is shown for each diastereomer (2*R*,3*R* for *trans* and 2*S*,3*R* for *cis*). The dominating *trans* form shows a larger ³J_{H2H3} scalar coupling. Signals between 1.5 and 2.2 ppm were only tentatively assigned

TABLE 1 Chemical shifts of the mixture of 2-ethoxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran diastereomers and comparison with values of *cis* and *trans* 2-benzoyloxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran from Yamamoto et al.¹⁹ and 2-methoxy-3,4-dihydro-3,5-dimethyl-2*H*-pyran from Descotes et al.²⁰

Atom	Observed (DMSO- <i>d</i> ₆) <i>trans</i>	Observed (DMSO- <i>d</i> ₆) <i>cis</i>	Yamamoto (CDCl ₃) <i>trans</i>	Yamamoto (CDCl ₃) <i>cis</i>	Descotes (CCl ₄) <i>trans</i>	Descotes (CDCl ₄) <i>cis</i>
H2	4.52, d, <i>J</i> = 4.6 Hz	4.73, d, <i>J</i> = 2.3 Hz	4.60, d, <i>J</i> = 4.0 Hz	4.79, d, <i>J</i> = 2.1 Hz	4.35, d, <i>J</i> = 3.4 Hz	4.52, d, <i>J</i> = 1.7 Hz
H3	1.5-2.2 ov ^a	1.5-2.2 ov ^a	1.98 dddt	1.90 m		
H41	1.5-2.2 ov ^a	1.5-2.2 ov ^a	2.24 dd	1.76 m		
H42	1.5-2.2 ov ^a	1.5-2.2 ov ^a	1.53 dd	0.96 m		
H6	6.02, d, <i>J</i> = 1.4 Hz	5.99, d, <i>J</i> = 1.4 Hz	6.03, d, <i>J</i> = 1.2 Hz	6.02, d, <i>J</i> = 1.2 Hz	5.91	5.91
H7	0.90, d, <i>J</i> = 6.9 Hz	0.92, d, <i>J</i> = 6.5 Hz	0.96, d, <i>J</i> = 7.0 Hz	1.00, d, <i>J</i> = 6.4 Hz	0.91-1.51	0.96-1.52
H8	1.50 ov	1.50 ov	1.54, d, <i>J</i> = 1.2 Hz	1.55, d, <i>J</i> = 1.2 Hz	0.91-1.51	0.96-1.52
H1'/H1''	3.50-3.70 ov	3.50-3.70 ov	4.82 d, 4.57 d	4.78 d, 4.55 d	3.32	3.33
H2'	1.13 ov	1.13 ov	-	-		
C2	100.1	97.9	99.8	97.8		
C3	29.9 ^b	30.5	30.3	31.0		
C4	29.8 ^b	29.4	30.2	29.7		
C5	107.0	108.1	108.2	109.7		
C6	134.1	134.0	134.0	133.8		
C7	16.2	15.8	16.5	16.2		
C8	18.0	17.9	18.4	18.3		
C1'	62.9	62.9	69.4	69.1		
C2'	15.0	14.9				

^aIndividual assignment could not be achieved because of overlapping signals (ov: overlap).

^bAssignment might be swapped.

with a ¹*J*_{CN} of 0.67 Hz observed for ¹⁵N-labelled pyridine.²⁶ The observed ¹⁵N resonance of -69.7 ppm referenced to CH₃NO₂ agrees well with previously reported chemical shifts measured at natural abundance.^{21,22} A comparison with ¹⁵N chemical shifts of other methyl-substituted pyridine derivatives is given in Supplementary Table S1.

In addition to NMR spectroscopy, mass spectrometry confirmed the chemical identity of compound **3**, whose mass spectrum differed from the unlabelled 3,5-dimethylpyridine,²⁷ only for the ¹⁵N-containing fragments.

3 | CONCLUSION

¹⁵N-labelled 3,5-dimethylpyridine could be conveniently synthesized in two steps starting from methacrolein, 1-ethoxypropene, and ¹⁵NH₄Cl.

4 | EXPERIMENTAL

Unlabelled reagents were purchased from Sigma-Aldrich. ¹⁵N-labelled NH₄Cl was purchased from Chemotrade Chemiehandelsgesellschaft (Leipzig, Germany).

4.1 | NMR spectroscopy and mass spectrometry

Unless stated otherwise, NMR spectra were recorded either on a Bruker AMX 500 or a Bruker AMSY 270 with CDCl₃ as solvent at 298K. ¹H and ¹³C chemical shifts were referenced to TMS. The solvent signals of signals were set for DMSO-*d*₆ to 2.49 ppm (¹H) and 39.51 ppm (¹³C) and for CDCl₃ to 7.24 ppm (¹H) and 77.2 ppm (¹³C). ¹⁵N resonances were indirectly referenced to CH₃NO₂, using a saturated solution of ¹⁵NH₄Cl in H₂O

(~5.64 M) with a chemical shift of -352.89 ppm.²⁸ Mass spectra were recorded on a Varian MAT 711.

4.2 | Synthesis of 2-ethoxy-3,4-dihydro-3,5-dimethyl-2H-pyran 13

14 g (0.2 mol) of methacrolein **11**, 26 g (0.3 mol) of 1-ethoxypropene **12**, and 0.1 g of hydroquinone (0.25% of mixture) were heated in a 200-ml autoclave (high-pressure laboratory autoclave model II from Carl Roth, Germany) at 190 °C for 16 hours. During that time, the pressure first rose to 15 bar and then fell to 8 bar. After cooling, the reaction mixture was distilled under reduced pressure of 48 mbar, yielding at 97°C 18.8 g of a fruity-smelling colorless oil. The product **13** was further purified by column chromatography (Al₂O₃, hexane/ethyl acetate 10:1, column dimensions 40 × 6 cm). Yield: 11.7 g (74.8 mmol; 37%). $n_D^{20} = 1.4420$. TLC (Al₂O₃ hexane/ethyl acetate 10:1): $R_f = 0.727$. ¹H-NMR (DMSO-*d*₆): 6.02 (s, 0.59H, H6trans), 5.99 (s, 0.41H, H6cis), 4.73 (d, 0.41H, H2cis, $J = 2.3$ Hz), 4.52 (d, 0.59H, H2trans, $J = 4.6$ Hz), 3.5-3.7 (m, 2H, CH₂CH₃), 1.5-2.6 (m, 3H, H3/H4), 1.5 (s, 3H, 5-CH₃), 1.12 (q, 3H, CH₂CH₃), 0.91 (2×d, 3H, 3-CH₃). ¹³C-NMR (DMSO-*d*₆): 134.1 (C6), 108.1 (C5cis), 107.0 (C5trans), 100.0 (C2trans), 97.9 (C2cis), 62.9 (CH₂CH₃), 29.4-30.4 (C3 and C4), 17.9 (5-CH₃), 16.2 (3-CH₃ trans), 15.7 (3-CH₃ cis), 15.0 (CH₂CH₃). MS (EI): 156 (18, M⁺), 111 (19), 86 (100, retro-Diels-Alder), 58 (90).

4.3 | Synthesis of 3,5-dimethylpyridine 3

In a three-necked flask equipped with a reflux condenser, an addition funnel, and a magnetic stirrer, 150 ml of deionized water were poured, followed by 4.4 ml of concentrated H₂SO₄, 15 g (39.7 mmol) of methylene blue, and 2 g (36.7 mmol) of ¹⁵NH₄Cl. The solution was brought to reflux, and a solution of 5.78 g (37 mmol) of 2-ethoxy-dihydro-3,5-dimethyl-2H-pyran **13** in 5 ml of ethanol was added dropwise over a period of 1 hour and refluxed for 17 hours. After cooling, 150 ml of deionized water was added and the mixture was distilled until the odor of glutaraldehyde disappeared in the distillate (ca. 200 ml). After cooling of the remaining reaction mixture, 250 ml of 1.3 M NaOH were added gradually and distilled until ~200 ml of distillate was collected. 0.1 g of Na₂CO₃ was added, and CH₂Cl₂ was used to extract the organic base. The combined organic layers were dried with Na₂SO₄, and the solvent was removed with a rotary evaporator. Yield: 2.18 g (20.2 mmol; 55%). ¹H-NMR (CDCl₃): 8.21 (d, 2H, H2/H6, ²J_{NH} = 10.6 Hz), 7.26 (s, 1H, H4), 2.25 (s, 6H, CH₃), ¹³C-NMR (CDCl₃): 147.3 (C2/C6), 137.0 (d,

³J_{NC} = 3.5 Hz, C4), 132.4 (d, ²J_{NC} = 3.1 Hz, C3/C5), 18.1 (CH₃). ¹⁵N-NMR (CDCl₃): -69.7 ppm referenced to CH₃NO₂. MS (EI): 108 (100, C₇H₉¹⁵N⁺), 93 (21), 79 (35), 77 (11).

ACKNOWLEDGEMENTS

We thank Dr Nadine Jagerovic, Dr Christophe Dardonville, and Dr Ibon Alkorta for their advice and fruitful discussions; Reinhard Zander for his valuable support and organization of the synthesis laboratory; Dr Alžbeta Krutošiková for translating a Czech publication; Ilya Shenderovich for his help accessing Russian references; Anja Peuker for providing details of the used instruments; and Dr Chiara Cabrele for comments on the manuscript. We acknowledge financial support from the European Commission, Brussels, within the European Human Capital & Mobility Network "Localization and Transfer of Hydrogen," Network Reference No. ERBCHRXT940582 and from the Deutsche Forschungsgemeinschaft, Bonn, Grant/Award Number: Li 300/29-1.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Schubert M, Limbach H-H, Elguero J. Synthesis of ^{15}N -labelled 3,5-dimethylpyridine. *J Label Compd Radiopharm*. 2019;62:914–919. <https://doi.org/10.1002/jlcr.3807>