Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXVIII, No. 4

A CONVENIENT PREPARATION OF 2-[^{15}N]-AMINO-4,6-DIMETHOXYPYRIMIDINE

Thomas K. Spencer†, Gunda I. Georg‡, and Jeffrey Aubé‡

†Oread Laboratories, Inc.
1501 Wakarusa Drive
Lawrence, Kansas 66046

Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas 66045

SUMMARY

A convenient preparation of 2-[^{15}N]-amino-4,6-dimethoxypyrimidine using ^{15}N-ammonium chloride as the source of ^{15}N is described.

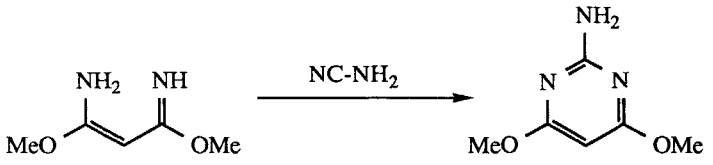
Key words: 2-aminopyrimidine, nitrogen-15, synthesis

We required a general route for the preparation of sulfonic amides of various labelled pyrimidines in connection with ongoing studies of the metabolism of various chemical classes containing this functional group. Since this linkage is most conveniently formed by the direct sulfonylation of a 2-aminopyrimidine moiety (1), convergency requires that access to the latter class of compounds specifically labelled at the 2-amino nitrogen be obtained. In particular, 2-[^{15}N]-amino-4,6-dimethoxypyrimidine ([^{15}N]-**1**) was sought for use in this context. Herein we describe an unambiguous synthesis of this compound which specifically places the label at the 2-amino nitrogen atom and allows the use of relatively inexpensive ^{15}N-ammonium chloride as the ^{15}N source.

A highly efficient synthesis of the desired title compound has been reported in the literature (2), and is shown in equation 1. However, it was felt that cyanamide would be an unsatisfactory starting material for labelled compound. While the mechanism of the reaction has been postulated to involve incorporation of one of the nitrogen atoms of the cyanamide into the ring and the other at the two position (3, 4), the use of ^{15}N-labelled cyanamide is untenable due to its propensity to undergo tautomeric scrambling (5, 6). Also, the cost of labelled cyanamide represented another negative feature of this approach.

0362–4803/90/040433–04$05.00

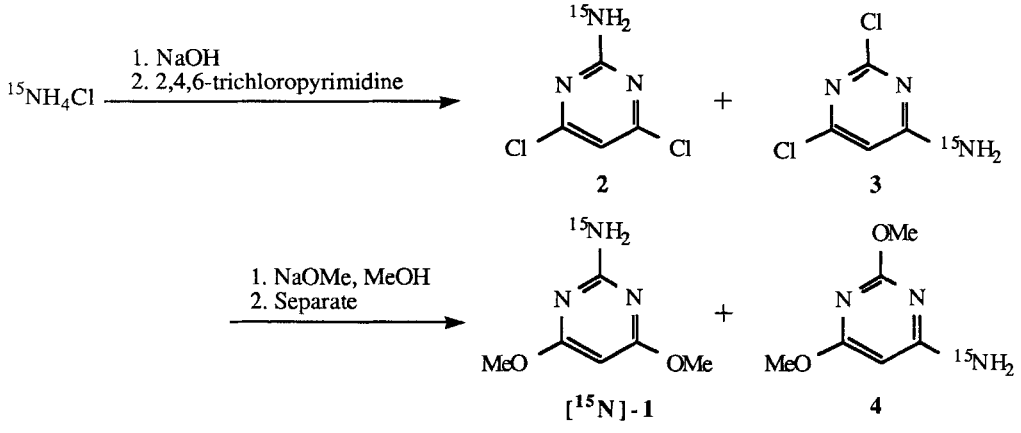
Revised September 29, 1989



(1)

1

Another route to the preparation of this heterocycle involves the addition of ^{15}N-labelled ammonia to the intact pyrimidine ring system by nucleophilic displacement of a chloride at the 2-position. A modification of the procedure of Büttner (7) was utilized to provide a mixture of aminodichloro isomers **2** and **3**, followed by displacement with alkoxide (Scheme 1) (8, 9).



Scheme 1

^{15}N-Labelled ammonia (3.0 equivalents) was treated with 2,4,6-trichloropyrimidine (Aldrich Chemical Company). This resulted in an approximately equimolar mixture of aminopyrimidines **2** and **3**. Extraction into benzene afforded an 85 : 15 mixture, which was directly treated with sodium methoxide in methanol to produce a quantitative mixture of isomeric aminodimethoxy pyrimidines **[^{15}N]-1** and **4**. The title compound **[^{15}N]-1** could be isolated by column chromatography and further purified by recrystallization from 2-propanol. The ^1H-NMR spectrum showed the expected ^{15}N-H (J = 88.9 Hz) coupling fully consonant with the structure depicted. None of the unlabelled isomer could be detected in the NMR spectrum as shown by comparison with unlabelled material. Thus, 2-amino-4,6-dimethoxypyrimidine was synthesized in 32% overall yield from 2,4,6-chloropyrimidine with complete positional integrity of the isotopic label.

EXPERIMENTAL

General. ^1H-NMR spectra were recorded on a Varian 80 MHz FT-80A spectrometer in

dimethylsulfoxide-d_6 solution using internal dimethylsulfoxide-d_5 as standard (δ 2.5). ^{15}N-Ammonium chloride was obtained from Isotech, Inc. in 99.8% isotopic purity; all other chemicals were purchased from Aldrich Chemical Company (Milwaukee, Wisconsin) and used as received. Thin layer chromatography (TLC) was carried out on precoated Whatman K6F silica TLC plates using 4:1 diethyl ether/benzene as eluent, and column chromatography was carried out using Merck Grade 60 silica gel using diethyl ether as eluent.

2-[^{15}N]-Amino-4,6-dichloropyrimidine (2) and 4-[^{15}N]-amino-2,6-dichloropyrimidine (3). A modification of the procedure of Büttner was followed (7). Sodium hydroxide (15.0 g, 0.380 mol) and ^{15}N-ammonium chloride (10.0 g, 0.186 mol) were ground separately with a mortar and pestle. The resulting powders were added to a single-neck, 100 mL flask, which was immediately connected to a gas outlet tube which led via Tygon tubing to a 250 mL flask (fitted with a magnetic stir bar and dry ice condenser) which contained 60 mL ethanol maintained at -78°C (dry ice/2-propanol). The solid mixture was shaken intermittently to generate ammonia gas, and was heated with a hot air gun until gas evolution was complete. The cooling bath was removed from the ethanol-ammonia solution, which was stirred and allowed to warm to room temperature. To this was added 2,4,6-trichloropyrimidine (11.4 g, 0.062 mol) dissolved in ethanol (ca. 6 mL) with stirring. The solution was stirred without external heating as the temperature rose to ca. 55° C over 15 minutes, resulting in a thick slurry which could not be stirred. After standing an additional 45 min, the mixture was filtered to give a white crystalline solid, which was stirred with water (75 mL) and filtered. Air drying overnight gave a product (10.61 g) which contained roughly equal amounts of the title compound along with 4-amino-2,6-dichloropyrimidine as determined by proton NMR. The products (20 g) from two runs of the above procedure were combined in a Soxhlet apparatus and extracted for 20 hours with benzene (200 mL). The benzene solution was allowed to cool to room temperature, resulting in the precipitation of the title compounds. Concentration gave a material (9.73 g, 0.059 mol) which consisted primarily of **2**, along with ca. 15% **3**. This product was used without further purification. For **2**: ^{1} NMR (80 MHz, DMSO) δ7.58 (d, J=90.2 Hz, 2H), 6.86 (s, 1 H); TLC R_f = 0.58. For **3**: ^{1} NMR: δ7.73 (d= 90.5 Hz), 6.45 (s, 1H); TLC R_f = 0.36.

2-[^{15}N]-Amino-4,6-dimethoxypyrimidine. The following was adapted from literature procedures (7,8). The product from the above procedure was dissolved in methanol (100 mL) and stirred under argon. Sodium methoxide (25% solution in methanol, 54.0 mL, 0.235 mol) was added rapidly, and the mixture was then heated to reflux for 9 hours, at which time the mixture was cooled and acetic acid (7 mL) added to quench excess methoxide. The reaction mixture was

concentrated, and partitioned between water (75 mL) and ether (50 mL); the aqueous layer was basicified using solid sodium carbonate. The phases were separated, and the aqueous portion extracted with ether (2 x 50 mL). The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and reduced in volume to give an oily residue. Azeotropic distillation with benzene afforded crude product (9.3 g) as a white crystalline solid. The solid was recrystallized from 2-propanol (90 mL) to give 5.37 g of **[^{15}N]-1**. The filtrate was reduced in volume to 50 mL and cooled to give an additional 1.95 g of solid. The filtrate was stripped of solvent to give an additional 0.89 g. The latter two quantities were separately chromatographed to give 2.02 g of product. The products from the crystallization and chromatography procedures were combined (7.39 g total) and recrystallized from 2-propanol to yield 6.30 g (32 % yield from trichloropyrimidine) of the title compound, m.p. 95-98° (lit.(8) 95°C): ^{1}H NMR: δ6.53 (d, J=88.9 Hz, 2H); 5.35 (s, 1H); 3.77 (s, 6H).

Acknowledgement: Financial support from Oread Laboratories, Inc. is gratefully acknowledged.

REFERENCES

1. (a) Lednicer D. and Mitscher L.A. - The Organic Chemistry of Drug Synthesis, Vol. 1, John Wiley and Sons, New York, 1977, pp. 261-267; Vol. 3, 1977, pp. 153-6. (c) Brown D. - Comprehensive Heterocyclic Chemistry, Katritzkky A.R. and Rees C.W., eds., Vol. 3, Pergamon Press, Oxford, 1984, pp. 57-155.

2. E.I. DuPont de Nemours and Co. - Israeli IL 61185 (1984); Chem. Abstr. 103: 87900k (1985)

3. Huffman K.R. and Schaefer F.C. - J. Org. Chem. 28: 1816 (1963)

4. Lwowski W. - Synthesis 263 (1971)

5. Plentl A.A. and Schoenheimer R. - J. Biol. Chem. 153: 203 (1944)

6. Omura A., Nanaka T., Fuchigami T., Ichikawa E. and Odo K. - Bull. Chem. Soc. Jpn. 50: 914 (1977)

7. Büttner E. - Chem. Ber. 36: 2227 (1903)

8. Fisher H.J. and Johnson T.B. - J. Am. Chem. Soc. 54: 727 (1932)

9. Rose F.L. and Tuey G.A.P. - J. Chem. Soc. 81 (1946)