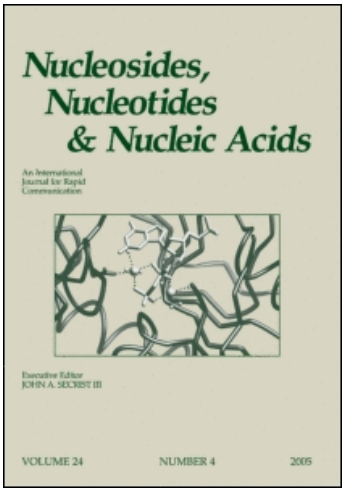


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

1-(5-Amino-1-β-D-Ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole, a new Intermediate for the Preparation of Aicar Analogs

Peter K. Bridson[a]; Rogers E. Harry O'Kuru[a]
[a] Department of Chemistry, Memphis State University Memphis, TN, USA

To cite this Article Bridson, Peter K. and O'Kuru, Rogers E. Harry(1991) '1-(5-Amino-1-β-D-Ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole, a new Intermediate for the Preparation of Aicar Analogs', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 355 — 358
To link to this Article: DOI: 10.1080/07328319108046478
URL: http://dx.doi.org/10.1080/07328319108046478

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 355-358 (1991)

1-(5-AMINO-1-β-D-RIBOFURANOSYLIMIDAZOL-4-CARBONYL)-3,5-DIMETHYLPYRAZOLE, A NEW INTERMEDIATE FOR THE PREPARATION OF AICAR ANALOGS.

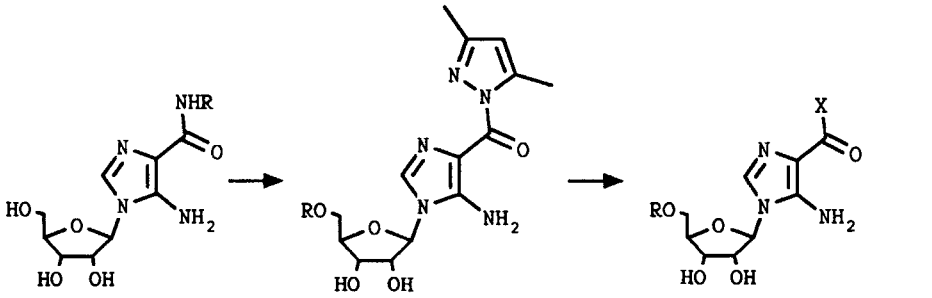
Peter K. Bridson* and Rogers E. Harry O'Kuru
Department of Chemistry, Memphis State University
Memphis, TN 38152, USA

Abstract: 1-(5-Amino-1-β-D-ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole (2a), which is readily prepared from inosine, is shown to be a useful precursor for the preparation of 5-aminoimidazole nucleosides and nucleotides.

SAICAR is an imidazole nucleotide which is an important intermediate in purine metabolism. Methods for the preparation of analogs of SAICAR have been limited due to several difficulties. The most direct approach, carbodiimide mediated coupling of an amine with the corresponding imidazolecarboxylic acid[1], suffers from low yields due to the instability of the acid, which readily loses carbon dioxide with subsequent decomposition of the remaining aminoimidazole. Several activated forms of the carboxylic acid have been prepared and shown to react directly with amines[2,3], but since these are formed from the carboxylic acid or its salt, overall yields are not high. The most important of these derivatives is the N-hydroxysuccinimidyl ester, but the lability of this compound precludes its phosphorylation prior to reaction with an amine. Difficulties have also been reported in phosphorylation of the preformed nucleoside analogs due to the reactivity of the amide group with phosphoryl chloride[3]. In light of these difficulties, and because we sought an activated derivative which could be prepared from a more readily available nucleoside precursor, we have explored the chemistry of the nucleoside pyrazolide (2a), which can readily be prepared from inosine.

Preparation of the N-tosyl amide (1a) from inosine, by a slight modification of the reported procedure[4] and without isolation of the intermediates, was accomplished in excellent yield. Reaction with

anhydrous hydrazine[4] yields the hydrazide (1b), which reacts with acetylacetone in the presence of an acid catalyst to give the pyrazolide in quantitative yield. Use of HCl as the catalyst results in the isolation of 2a as its hydrochloride salt, which can be crystallized from ethanol and stored indefinitely. When acetic acid is used, the neutral compound is isolated as an amorphous, hygroscopic powder. The free base can also be liberated from the hydrochloride by treatment with sodium bicarbonate. The structure of 2a was confirmed by spectroscopy and analysis, and by reaction with ammonia. AICA riboside (3a) was isolated and shown to be identical with an authentic sample. Also isolated and characterized was 3,5-dimethylpyrazole.



1a. R = Ts
1b. R = NH_2

2a. R = H
2b. R = PO_3H_2

3a. R = H, X = NH_2
3b. R = H,
X = $NHCH_2CH(OEt)_2$
3c. R = PO_3H_2,
X = NH_2

Reaction of the pyrazolide with primary and secondary amines was found to take place readily at elevated temperatures. The most convenient procedure was to dissolve the pyrazolide in an excess of the amine, and to heat the mixture at 70°C under nitrogen. Reaction was usually complete in less than one hour. Preparation of the acetal (3b) is illustrative. Alternatively, the nucleoside and the amine could be dissolved in a minimum quantity of anhydrous DMF. The pyrazolide was also found to react with alcohols, in the presence of triethylamine, to yield esters.

The significant advantage of the pyrazolide (2a) over related activated derivatives of AICA riboside is demonstrated by its phosphorylation. Reaction with phosphoryl chloride in trimethyl phosphate[5] gives the nucleotide in excellent yield. Proton and P-31 NMR spectra of the product clearly indicate that it is the 5′-phosphate (2b), *isolated as an internal salt*. Reaction with ammonia gives AICAR (3c), identical with an authentic sample. We are currently exploring the preparation of SAICAR analogs from this nucleotide.

EXPERIMENTAL

1-(5-Amino-1-β-D-ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole (2a). 5-Amino-1-β-D-ribofuranosylimidazole-4-carbohydrazide (1.0g, 3.7mmole) was dissolved in 0.5M hydrochloric acid (30mL), and 2,4-pentanedione (1.0mL, 9.7mmole) was added. The solution was stirred at room temperature for 1 h, then washed with dichloromethane and concentrated in vacuo. The solid residue (1.2g, 97% yield) was crystallized from absolute ethanol to give an analytical sample of the hydrochloride salt, mp. 167-8°C. ^{1}H NMR (D_2O): 2.15 (s,3H,CH_3), 2.4 (s,3H,CH_3), 3.8 (m,2H,H-5′), 4.25 (m,1H,H-4′), 4.3 (m,1H,H-3′), 4.55 (m,1H,H-2′), 5.8 (d,1H,H-1′), 6.05 (s,1H,pyr-H), 8.6 (s,1H,imid-H). Anal. calcd. for $C_{14}H_{19}N_5O_5$.HCl: C, 44.98; H, 5.39; N, 18.74; found: C, 44.68; H, 5.52; N, 18.47.

2-(5-Amino-1-β-D-ribofuranosylimidazol-4-carbonyl)aminoacetaldehyde diethyl acetal (3c). A mixture of 1-(5-Amino-1-β-D-ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole (1.2g, 3.6mmol) and 2-aminoacetaldehyde diethyl acetal (3.2mL, 22mmol) was heated at 70°C for 0.5h. The mixture was cooled and added slowly to rapidly stirred diethyl ether (400mL). The solid was filtered, washed with ether, and dried to yield 1.1g (82%). An analytical sample had mp. 145-146°C. ^{1}H NMR (DMSO-d_6): 1.1 (t,6H, CH_3), 3.3 (t,2H,NHC<u>H</u>$_2$CH), 3.55 (m,6H,OCH_2 and H-5′), 3.9 (m,1H,H-4′), 4.05 (m,1H,H-3′), 4.3 (m,1H,H-2′), 4.6 (t,1H,NHCH$_2$C<u>H</u>), 5.2 (d,1H,3′OH), 5.3 (t,1H,5′OH), 5.4 (d,1H,2′OH), 5.5 (d,1H,H-1′), 5.9 (br s,2H,NH_2), 7.2 (t,1H,N<u>H</u>CH$_2$CH), 7.35 (s,1H,H-2). Anal. calcd. for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.97; found: C, 48.29; H, 7.13; N, 15.01.

1-[5-Amino-1-(5-phosphono-β-D-ribofuranosyl)imidazol-4-carbonyl]-3,5-dimethylpyrazole (2b). 1-(5-Amino-1-β-D-ribofuranosylimidazol-4-carbonyl)-3,5-dimethylpyrazole (0.2g, 0.6mmol) was dissolved in trimethyl phosphate (1mL), and the solution was cooled to 0°C. Phosphoryl chloride (0.1mL) was added and the mixture was stirred for 4h. Water was added and the solution was kept for 2h, with occasional addition of 6M sodium hydroxide to keep the pH around 4. Solvents were evaporated in vacuo, and the product was precipitated by addition of ethanol, filtered, and dried to yield 0.2g (80%). ^{1}H NMR (D_2O): 2.15 (s,3H,CH_3), 2.4 (s,3H,CH_3), 4.1 (m,2H,H-5′), 4.3 (m,2H,H-3′and 4′), 4.6 (m,1H,H-2′), 5.85 (d,1H,H-1′), 6.1 (s,1H,pyr-H), 8.6 (s,1H,imid-H).

REFERENCES

1. Shaw, G.; Thomas, P. S.; Patey, C. A. H.; Thomas, S. E. *J. Chem. Soc. Perkin Trans. I* **1979**, 1415.
2. Srivastava, P. C.; Mancuso, R. W.; Rousseau, R. J.; Robins, R. K. *J. Med. Chem.* **1974**, *17*, 1207.
3. Burrows, I. E.; Shaw, G.; Wilson, D. V. *J. Chem. Soc. (C)* **1968**, 40.
4. Shaw, E. *J. Am. Chem. Soc.* **1959**, *81*, 6021.
5. Yoshikawa, M., Kato, T., Takenishi, T. *Bull. Chem. Soc. Japan* **1969**, *42*, 3505.