ISSN: 2161-1009
Biochemistry & Analytical Biochemistry

OPEN ACCESS Freely available online

Commentary

Synthesis of Chirality Amino Acids Under Biological Conditions

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ABOUT THE STUDY

Amino acids are among the essential chemical building blocks of life. These structures are embedded in many small molecule pharmaceuticals and are the primary components of peptide-based therapeutics and biologics. Iso topically labeled a-amino acids and their derivatives have widespread use in structural and mechanistic biochemistry, quantitative proteomics, Absorption Distribution Metabolism and Excretion (ADME) and as imaging agents in Positron Emission Tomography (PET) techniques. The preparation of carbon-labeled a-amino acids remains difficult and time consuming, with established methods involving label incorporation at an early stage of synthesis.

This explains the high cost and scarcity of C-labeled products and presents a major challenge in 11C application. Here we report that simple aldehydes catalyze the isotopic carboxylate exchange of native a-amino acids with CO_2. Protein organic-amino acids and many non-natural variants containing diverse functional groups undergo labeling. The reaction likely proceeds *via* the trapping of by imine-carboxylate intermediates to generate aminomalonates that are prone to mono decarboxylation. Tempering catalyst electro philicity was to preventing irreversible aldehyde consumption. The pre-generation of the imine carboxylate intermediate allows for the rapid and late-stage 11C-radiolabeling of a-amino acids in the presence of CO_2.

The preparation of molecular targets where a native isotope is substituted with a heavier or radioactive isotope is essential to drug development and medical imaging. It is often preferable to use carbon-based isotope labels rather than hydrogen iso troopers because carbon labels are not prone to washing out, and they do not cause metabolic shifting. Despite over 70 years of study, the synthesis of a-amino acids incorporating carbon isotopes remains a challenge and generally involves the early introduction of the C label into a precursor molecule followed by several additional synthetic steps.

Representative methods include substitution or addition reactions of electrophiles with CN-sources, the early-stage addition of simple alkyl or aryl organometallics to CO_2, alkylation using labeled electrophiles like CH3l, and sequences that start with C-acetate. Auxiliary-controlled asymmetric syntheses of C-amino acids exist; however they occur with low to moderate radiochemical yields and require time-consuming, multi-step approaches. The biosynthesis of labeled a-amino acids by fermentation in the presence of C-glucose or C-acetate is possible but requires specialized equipment, carefully optimized pilot studies, and tedious isolation and purification of labeled products.

Furthermore, the short half-life of 11C (20 minutes) makes the multi step preparation of amino acid targets needed for PET problematic. Current approaches are restricted to cyanation hydrolysis reactions using 11CN, and for certain products like 11C-methionine, methylation with CH3l. Additionally, 11C glutamine or glutamate can be prepared by conjugate additions of 11C acrylates. In this, a general approach to prepare C-labeled a-amino acids that uses a late-stage label incorporation strategy conceptually analogous to hydrogen isotope exchange would help accelerate drug development and would allow the expansion of amino acid radiotracers in PET imaging.

Carbon dioxide is the primary source of all iso topically labeled carbon reagents. The use of CO_2 in late-stage labeling applications is difficult because of the lack of methods for its effective capture and incorporation without resorting to the use of highly nucleophilic reaction intermediates and large excesses of CO_2. It's established that certain electronically stabilized carboxylic acids, like aryl acetates and malonic half-esters, undergo reversible decarboxylation in polar aprotic solvents. Amino acids lack the required anion stabilizing ability to undergo decarboxylation under normal laboratory conditions and their spontaneous decarboxylation is exceptionally slow. Net carboxylate exchange reactions 34 of carboxylic acids using N-hydroxyphthalimide derivatives in the presence of Ni-promoters can be used to generate C5 labeled glutamic acid, however C1-carboxylate and amino group protection is required and the process is not general for other amino acids.

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Received: 31-Mar-2022, Manuscript No. BABCR-22-16611; **Editor assigned:** 04-Apr-2022, PreQC No. BABCR-22-16611 (PQ); **Reviewed:** 19-Apr-2022, QC No. BABCR-22-16611; **Revised:** 26-Apr-2022, Manuscript No. BABCR-22-16611 (R); **Published:** 03-May-2022, DOI: 10.35248/2161-1009-22.11:427.

Citation: Schuster S (2022) Synthesis of Chirality Amino Acids Under Biological Conditions. Biochem Anal Biochem. 11:427.