

Citation Classics

Simon E J & Shemin D. The preparation of S-succinyl coenzyme A.
J. Amer. Chem. Soc. 75:2520, 1953.

The authors present a method for the synthesis of succinyl coenzyme A (succinyl CoA) by addition of succinic anhydride to CoA in the presence of a weak base. The anhydride method is applicable to the synthesis of other acyl derivatives of CoA. [The SC[®] indicates that this paper was cited 621 times in the period 1961-1976.]

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"Late in 1951, with a fresh Ph.D. in Organic Chemistry, I arrived in the laboratory of Dr. David Shemin at Columbia College of Physicians and Surgeons. The object of my post-doctoral fellowship was to train in biochemistry, a field which appeared to me much more exciting than organic chemistry.

"Coenzyme A (CoA) had been discovered rather recently in Dr. Fitz Lipmann's laboratory and 'active acetate' had been shown to be acetyl CoA by Dr. Feodor Lynen. It had become quite clear that acyl CoA derivatives were the substrates of a large number of enzymes important to intermediary metabolism. Dr. Shemin had just proved that the first step in porphyrin synthesis was the condensation of succinyl CoA with glycine. It occurred to us that a simple chemical synthesis of succinyl CoA, preferably one applicable to other acyl CoA derivatives would therefore be extremely useful to many investigators.

"Since CoA was very expensive, all initial experiments were done with glutathione (GSH). It soon became evident that the sulfhydryl groups disappeared rapidly when succinic anhydride was added to GSH solution in the presence of a weak base. Only a slight

excess of anhydride was needed for an essentially quantitative reaction. The product gave a hydroxamic acid test under conditions that suggested the presence of a thioester. Repetition of the experiment with CoA gave similar results.

"A crucial question remained: Did the succinic anhydride esterify other functional groups present in CoA and thereby destroy its activity? This question was best answered by determining whether our product was biologically active.

"I contacted Dr. Charles Gilvarg, who at that time was a post-doctoral fellow in Dr. Severo Ochoa's laboratory at NYU. Professor Ochoa and his collaborators, Cilbarg, Seymour Kaufman, Minor Coon and the late Joseph Stern, were anxious to test our synthetic material. They were working with several enzymes for which succinyl CoA was a substrate. Our material was quickly found to be biologically active. We went on to show that the method was applicable to the acylation of CoA by just about any acid for which an anhydride was available.

"In discussing the work with a number of distinguished biochemists, it became evident that many of them had thought of this simple approach but dismissed it since 'anhydrides would surely react with all kinds of functional groups present in the CoA molecule.' The biological innocence of an organic chemist and the carefree approach of youth overcame the hesitations, and the experiment that 'could not work' was carried out.

"The timing of this work was perfect since the demand for acyl CoA derivatives was world-wide. Publication of this extremely simple but useful synthesis provided a fine start for a young organic chemist who wanted to embark on a career in biochemistry. My everlasting thanks go to my mentor, David Shemin, whose encouragement, stimulating discussions and wide knowledge of biochemistry made this work possible and started me on a satisfying and exciting career."