

König W & Geiger R. Eine neue Methode zur Synthese Von Peptiden: Aktivierung der Carboxylgruppe mit Dicyclohexylcarbodiimid unter Zusatz von 1-Hydroxy-benzotriazolen. (A new method for synthesis of peptides: activation of the carboxyl group with dicyclohexylcarbodiimide using 1-hydroxybenzotriazoles as additives.) *Chem. Ber.* 103:788-98, 1970. [Hoechst AG, Frankfurt am Main, Federal Republic of Germany]

1-Hydroxybenzotriazole and a number of substituted 1-hydroxybenzotriazoles are suitable additives in the synthesis of peptides using the dicyclohexylcarbodiimide method.¹ These additives considerably reduce racemisation as well as the formation of by-products and provide peptides in excellent yield and a high state of purity. [The *SCI*[®] indicates that this paper has been cited in over 680 publications since 1970.]

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"R. Geiger and I started our careers as peptide chemists in the laboratories of Friedrich Weygand (Geiger in 1954 at Tübingen and Berlin and I in 1962 at Munich). There I investigated the rate of racemisation during peptide synthesis. For this purpose I developed, in collaboration with A. Prox, a sensitive and versatile gas chromatographic racemisation test.² In 1965, I joined the department of pharmaceutical research at Hoechst AG, where I met Geiger, who had made that step eight years before. One of our tasks was to develop new methods in peptide chemistry, thus accompanying the work of our admired teacher, Weygand, which we continued after his deplorable death in 1969. Concerning the rate of racemisation, Weygand already observed the beneficial effect of the addition of several N-hydroxy compounds to dicyclohexylcarbodiimide, the convenient peptide-forming reagent. We also tested many compounds as potential additives to dicyclohexylcarbodiimide,

but the results were discouraging. One day I glanced by chance at an advertisement of my principal, Hoechst AG, showing the formula of benzotriazole. I was immediately fascinated by the idea that the 1-hydroxy-derivative should comprise structural elements most favourable for our purposes. In a matter of days we showed in preliminary tests that 1-hydroxybenzotriazole was indeed the additive we had looked for the whole time.

"In 1969, I reported this result at the European Peptide Symposium in Abano Terme. It was well accepted by the audience and broadly applied immediately. In 1973, an outline of 1-hydroxybenzotriazole in peptide synthesis appeared in Japanese.³

"The simple synthesis of 1-hydroxybenzotriazole and its availability from suppliers of fine chemicals resulted in a reserve of another compound, 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, the use of which is sometimes more advantageous than 1-hydroxybenzotriazole. We frequently use this additive in segment condensation, but most peptide chemists are apparently not aware of the advantages of this compound, possibly also because they overvalue a minor side reaction, which we described in another paper.⁴

"I think that the report about 1-hydroxybenzotriazole in peptide synthesis became a *Citation Classic* because the reagent is easily accessible and application ensures optimal conditions for peptide synthesis in most cases. The method is so well established that citation is often omitted or secondary literature is cited as, e.g., in the *Pierce Handbook and General Catalog 1979-80*.⁵ It is thus the more surprising that such a high citation rate is found."

1. Sheehan J C & Hess G P. Letter to editor. (A new method of forming peptide bonds.) *J. Amer. Chem. Soc.* 77:1067-8, 1955.
2. Weygand F, Prox A & König W. Racemisierung bei Peptidsynthesen. *Chem. Ber.* 99:1451-60, 1966.
3. Munekata E & Sakakibara S. Use of 1-hydroxybenzotriazole in peptide synthesis. *J. Syn. Org. Chem. Jpn.* 31:853-8, 1973.
4. König W & Geiger R. Eine neue Methode zur Synthese von Peptiden: Aktivierung der Carboxylgruppe mit Dicyclohexylcarbodiimid und 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazin. *Chem. Ber.* 103:2034-40, 1970. [The *SCI* indicates that this paper has been cited in over 65 publications since 1970.]
5. 24460. 1-Hydroxybenzotriazole monohydrate (HBT). *Pierce handbook and general catalog 1979-80*. Rockford, IL: Pierce Chemical Co., 1979, p. 333.