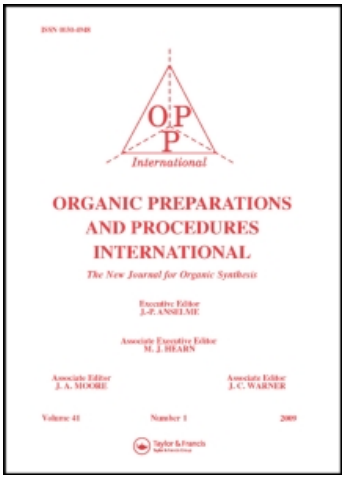


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION AND PROPERTIES OF N-α-CARBOBENZOXY-N-IMIDAZOLE ADAMANTYLOXYCARBONYL-L-HISTIDINE

Manohar A. Tilak[a]; Ralph Russell[a]; Mary L. Hendricks[a]
[a] The Lilly Research Laboratories, Indianapolis, Indiana

To cite this Article Tilak, Manohar A. , Russell, Ralph and Hendricks, Mary L.(1971) 'PREPARATION AND PROPERTIES OF N-α-CARBOBENZOXY-N-IMIDAZOLE ADAMANTYLOXYCARBONYL-L-HISTIDINE', Organic Preparations and Procedures International, 3: 1, 17 — 20
To link to this Article: DOI: 10.1080/00304947109356025
URL: http://dx.doi.org/10.1080/00304947109356025

ORGANIC PREPARATIONS AND PROCEDURES INT. 3(1), 17-20 (1971)

PREPARATION AND PROPERTIES OF N-α-CARBOBENZOXY-N-IMIDAZOLE ADAMANTYLOXYCARBONYL-L-HISTIDINE

Manohar A. Tilak, Ralph Russell, and Mary L. Hendricks
The Lilly Research Laboratories
Indianapolis, Indiana 46206

Protective groups for the imidazole function of histidine are not satisfactory for some syntheses. The benzyl group[1] is often employed; however, the use of im-benzyl* is limited by the low solubility of Z-(im-benzyl)-L-histidine owing to its zwitterionic nature. In addition, vigorous conditions (Na/liquid ammonia) may be necessary for the removal of the benzyl group in the event catalytic hydrogenolysis fails as has been observed with some peptides.[2]

Disubstituted derivatives such as Di-Z, Di-AdOC, Di-BOC[3-5] have been reported; however, both N-α and N-im protections are removed under the same conditions limiting the use of these derivatives to synthesis of peptides in which histidine is N-terminal. The imidazole-Z-group of Di-Z-L-histidine is not stable owing to its reactivity which may lead to acylation.[6]

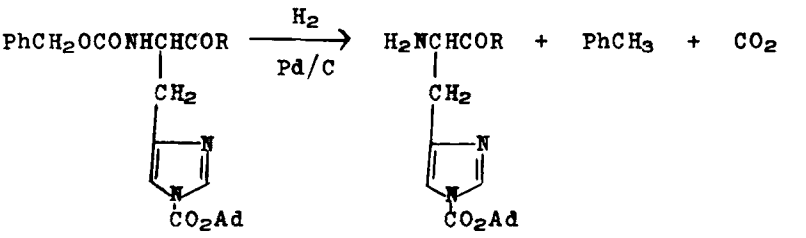
Weygand and Steglich[7] have introduced the use of 2,2,2-trifluoroethyl-1-acylamino groups which are stable to conditions required for removal of N-αZ or BOC protection groups

*Abbreviations: AdOC=adamantyloxycarbonyl; BOC=t-butyloxycarbonyl; im=imidazole; Z=benzyloxycarbonyl(carbobenzoxy)

enabling the use of these new groups for im protection while elongating peptide chains.

The synthesis of Z-(im-BOC)-histidine with BOC azide using Schnabel's (NaOH with pH Stat)[8] and Schwyzer's (magnesium hydroxide)[9] general procedures for making Nα-BOC derivatives of amino acids was unsuccessful and resulted in the imidazole catalyzed hydrolysis of the azide as judged by the consumption of the base.

We now report the successful synthesis of Z-(im-AdOC)-L-histidine; it was also found that Z-(im-AdOC)-L-histidine is readily soluble and easily undergoes catalytic hydrogenolysis with Pd/carbon as illustrated below.



(R = OH, OCH_3, other esters, NHR_2, etc., Ad = )

The AdOC group is not removed during this deblocking which frees the α-amino group for further reactions such as coupling with protected amino acids, activated esters, or mixed anhydrides.

Schnabel has reported that the im-BOC moiety (which is similar to AdOC-) is reasonably stable to aminolysis during peptide synthesis,[5] and the bulkiness of the adamantyloxy-carbonyl group might render the im-AdOC moiety even more

stable than im-BOC to such conditions.

EXPERIMENTAL

Preparation of Z-(im-AdOC)-L-Histidine - To a cold (0°) solution of 10 g (34.6 mmoles) Z-L-histidine in 34.6 ml (34.6 mmoles) of 1N NaOH was added 5.5 g Na_2CO_3 and 11.2 g (50 mmoles) adamantyloxycarbonyl chloride[4] in ~30 ml dioxane in 5 portions over a 1-hour period. Overnight, some solid separated which could not be dissolved by addition of ether, dioxane, or H_2O. The aqueous phase was extracted with three 50-ml. portions of ether, and the ethereal phase was discarded. The organic solvents were removed from the aqueous phase with a rotary evaporator. The aqueous phase was acidified to pH 2 with solid citric acid and then was extracted with ethyl acetate. The extract was washed three times with saturated KCl solution and twice with H_2O. The dried ($MgSO_4$) solution was evaporated yielding 10.6 g (47%) of a semi-solid oil. (The yield using pH stat. at 8.15 was ~90% crude solid).

The oil was dissolved in ether and dicyclohexylamine was added; the salt which solidified overnight was filtered and recrystallized from MeOH and H_2O to give product, mp. 125°, 9.35 g (64%).

Anal. Calcd. for $C_{37}H_{52}N_4O_6$: C, 68.49; H, 8.08; N, 8.64.
Found: C, 68.65; H, 8.15; N, 8.84.

Z-(im-AdOC)-L-histidine obtained from the salt by acidification with citric acid, extraction with EtOAc and evaporation, was chromatographically (TLC) pure and separable from Z-L-histidine. The NMR showed the expected pattern.

The IR spectrum showed the anticipated additional carbonyl peak at 1780 cm^{-1} as compared to Z-L-histidine.

REFERENCES

1. V. du Vigneaud and O. K. Behrens, J. Biol. Chem., 117, 27 (1937).
2. R. H. Mazur, Can. J. Chem., 40, 1098 (1962).
3. A. Patchornick, A. Berger, and E. Katchalaski, J. Am. Chem. Soc., 79, 6416 (1957).
4. W. L. Haas, E. V. Krumkalns, and K. Gerzon, ibid., 88, 1988(1966).
5. E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke, I. Ugi, "Tert. Butyloxycarbonylfluorid...", Peptides, E. Bricas, Ed., North Holland Publishing Co., Amsterdam, 1968, pp. 91-97.
6. M. Bodanszky and M. A. Ondetti, "Peptide Synthesis", Wiley and Sons, Inc., New York, 1966, p. 28.
7. F. Weygand, W. Steglich, and P. Pietta, Tetrahedron Letters, 31, 3751 (1966).
8. E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke, I. Ugi, Ann., 716, 175 (1968).
9. R. Schwyzer, P. Sieber, and H. Kappeler, Helv. Chim. Acta., 42, 2622 (1959).

(Received July 13, 1970)