Tetrahedron Letters Vol. 22, pp 185 - 186 0040-4039/81/0115-0186$02.00/0

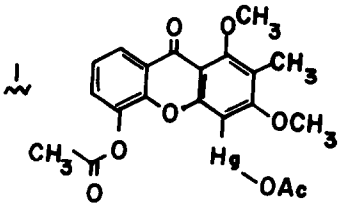
MODELS THAT DEMONSTRATE PEPTIDE BOND FORMATION BY PRIOR THIOL CAPTURE--II CAPTURE BY ORGANOMERCURY DERIVATIVES

D.S. Kemp* and Daniel J. Kerkman

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

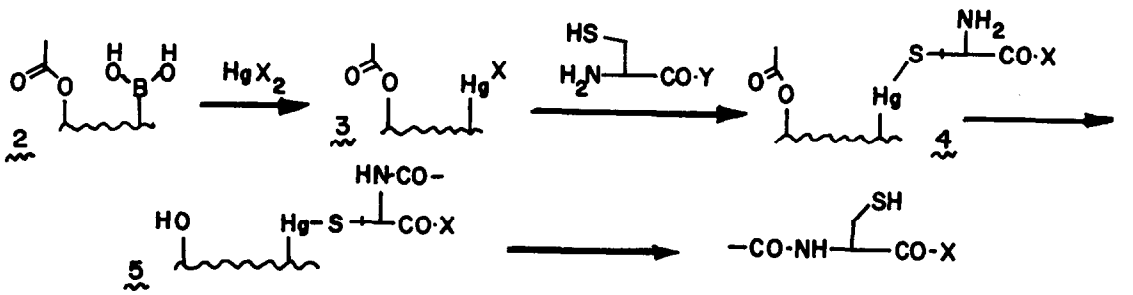
Abstract: The mercaptide derived from 5-acetoxy-1,3-dimethoxy-2-methylxanthone-4-mercuriacetate and ethyl cysteinate has been found to undergo intramolecular O,N-acetyl transfer with half times of 24 h and 8 h in DMF and DMSO, respectively. This result demonstrates the feasibility of peptide bond formation by prior thiol capture at an organomercuric site.

In the accompnaying paper we outline a general scheme for amide formation by thiol capture. In essence, peptide fragments bearing reactive amine and acyl functions are linked by a process of greater intrinsic affinity than the weak and unreliable interaction of a peptide amine with an electrophilic acyl function. The resulting molecule can then undergo an intramolecular acyl transfer, forming amide. Given its speed, reversibility with thiols and other reagents, and high affinity,[1] the reaction of organomercury derivatives with thiols is a natural candidate for this capture step. Before this tactic can be considered seriously, intramolecular acyl transfer via the large ring necessitated by the linear C-Hg-S geometry and long mercury bonds must be demonstrated.



Substance 1,[2] prepared by reaction of 5-acetoxy-1,3-dimethoxy-2-methylxanthone with mercuric acetate (175°C 4 min), was found to react immediately at 10^{-2} to 10^{-3} M concentration in DMF or DMSO with an equivalent of ethyl cysteinate to give a solution that is not colored by diphenylcarbazone, indicating that formation of the mercaptide is complete under these conditions.

Acyl transfer was followed by UV, TLC, and ^{1}H NMR spectroscopy; the rates in a given solvent were independent of concentration (indicating that the reactions are intramolecular), and half times at 25°C in DMF and DMSO of 24 h and 8 h, respectively, were observed. When 23 mg of 4 was allowed to react in DMF at 0.03 M concentration for 4 d, acidified, extracted (CH_2Cl_2), oxidized with iodine, quenched with ascorbic acid, 2 mg (28%) of diacetyl-L-cystine diethyl ester was isolated (PLC) and identified (spectroscopic and mixture mp). The electron-donating groups of 1 are artifacts of its availability in few steps from a known xanthone; their presence has the undesirable effect of greatly increasing the lability of the C-Hg bonds of its mercaptide complexes. Work is in process to achieve an increase in transfer rate and mercaptide stability with related structures.



Phenyl-mercury bonds are not likely to resist the acidic conditions used in many operations of peptide synthesis. In a practical capture strategy, the capture site must be attached to the carboxyl terminus of a fragment at a stage prior to the capture step. Thus it is likely that the mercury would be best introduced immediately before this step. The tactical sequence 2 → 3 → 4 → 5 may permit this introduction, given the quantitative conversion under mild, aqueous conditions of phenylboronic acids to phenylmercuric halides[3] and the demonstrated compatibility of phenylboronic acids with the operations of peptide synthesis.[4]

Acknowledgements

References:

1. R.B. Simpson, J. Amer. Chem. Soc., 83, 4711 (1961).
2. Satisfactory elemental analysis obtained for the dihydrate.
3. A. Michaelis and P. Becker, Chem. Ber., 15, 182 (1882).
4. D.S. Kemp and D.C. Roberts, Tetrahedron Letters, (1975) 4629.

(Received in USA 25 September 1980)