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A GENERAL AND VERSATILE ROUTE TO "ZINC FINGER" TEMPLATES

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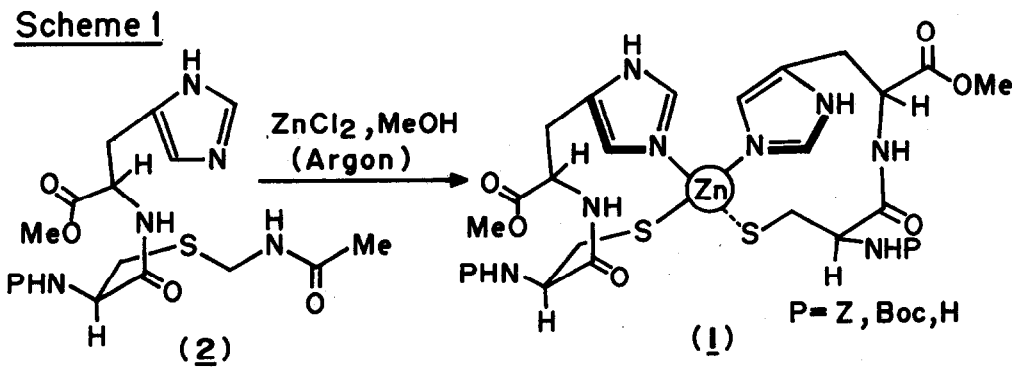
Abstract: The basic zinc finger template is formed in a single step from PNHCys[S-CH_2NHAc]HisOMe and zinc chloride by a tandem complexation deprotection sequence.

The first synthesis of a zinc finger template prototype represented by structure (1) was recently reported by us[1]. Crystallographic studies tend to show that the binding energy contribution of the zinc finger template plays a pivotal role in properly orienting the peptide recognition loop towards the major groove of B-DNA[2]. Compound (1) induces ordered conformational changes with poly d(G-C) and not with poly d(A-T), in line with expectations[3]. This finding provided impetus to delineate methodologies that would enable ready incorporation of peptide linker and recognition elements to reach our eventual goal, namely, the construction of discrete zinc finger motifs, an objective of current interest, in endeavours to correlate peptide sequences and their secondary structures to DNA sequences[1,2]. This objective can now be reached by a novel strategy, which is here illustrated with the synthesis of (1)[P=Z,Boc,H][4].

S-Acetamidomethyl-L-cysteine[5] was transformed to ZNHCys[SCH_2NHAc]-OH and condensed with histidine methyl ester to afford, ZNHCys[SCH_2-NHAc]HisOMe(2),mp 110-112°C[6]. Fortuitously, the (2)⟶(1) [P=Z] change was accomplished in a single step, in 92% yields, on treatment with methanolic anhydrous $ZnCl_2$ under argon[Scheme 1][7,8].

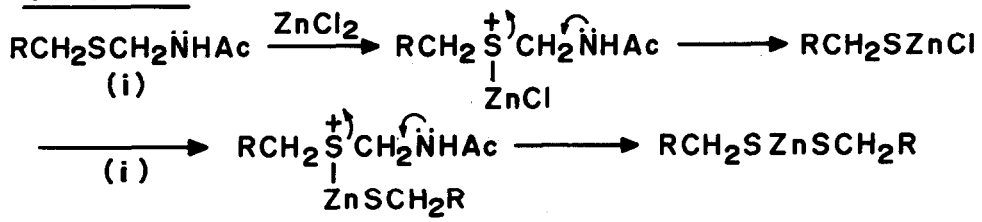
Scheme 1



The (2)⟶(1) change can be rationalized on the basis of a tandem

complexation - deprotection sequence[Scheme 2].

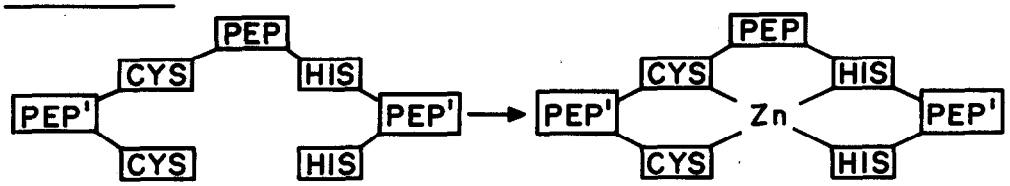
Scheme 2



Template (1) prepared by this procedure, in an overall yield of 10% from cysteine, was found identical in all respects to the earlier sample[1]. BocNHCys[SCH_2NHAc]HisOMe(3), mp 135-138°C, when processed as in Scheme 1, afforded template (1)(P=Boc)[mp 260-270°C, yield 80%], which on treatment with TFAA-H_2O gave (1)(P=H), as the TFA salt mp 235-240°C, in quantitative yields.

The strategy to zinc finger templates presented here (Scheme 1), will find application, since it permits, inter alia, the incorporation of peptide linker and recognition elements between the N-terminal cysteine and the C-terminal histidine, as illustrated in Scheme 3.

Scheme 3



CYS:CYSTEINE HIS:HISTIDINE PEP':LINKER (~3 RESIDUES)
PEP: RECOGNITION ELEMENT (~12 RESIDUES)

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1. Ranganathan,S.; Jayaraman,N.; Roy,R. Tetrahedron,1992,48,931.
2. Paveletich,N.P.; Pabo,C.O. Science,1991,252,809.
3. Dr.D. Chatterji, CCMB, Hyderabad, Private communication; also please see ref 1, footnote 1.
4. All the compounds presented here have been fully characterized [ir,nmr,FAB ms,analysis].
5. Milkowski,J.D.; Veber,D.F.; Hirschmann,R. Org.Syn.Coll.Vol.VI,p.5.
6. via p-nitrophenyl ester[DCC,EtOAc,0°/3h,rt/30h], mp 102-105°C, followed by reaction with HisOMe.2HCl[Et_3N,CH_2Cl_2,0°/3h,rt/30h].
7. Under argon, (2) in MeOH(5ml/mmol) was admixed with 0.2 M methanolic anh $ZnCl_2$(2 eq), left stirred 10h, adjusted to pH 8(aq NH_3,5%), filtered, washed with H_2O, hot MeOH and dried to afford (1)(P=Z).
8. Interestingly, the originally planned, logical, sequence for the (2)⟶(1) change, namely, deprotection($AgNO_3$), SH generation(H_2S) and complexation($ZnCl_2$), gave intractable mixtures.

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