

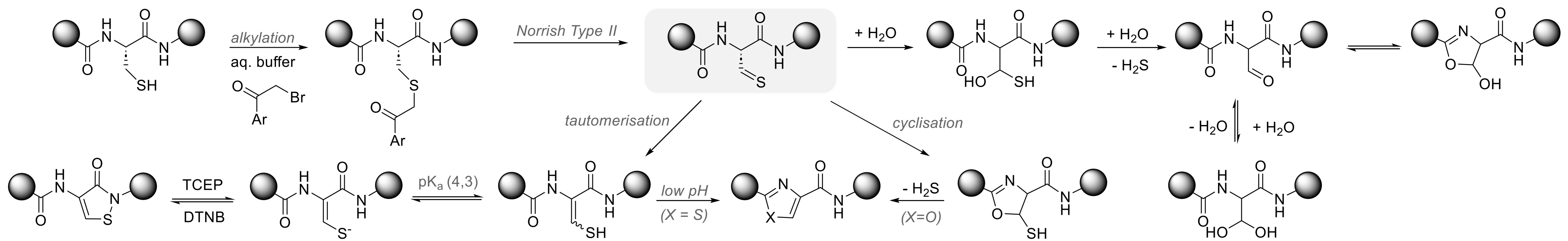
# On-Resin Synthesis and Modification of Novel Peptide Heterocycles

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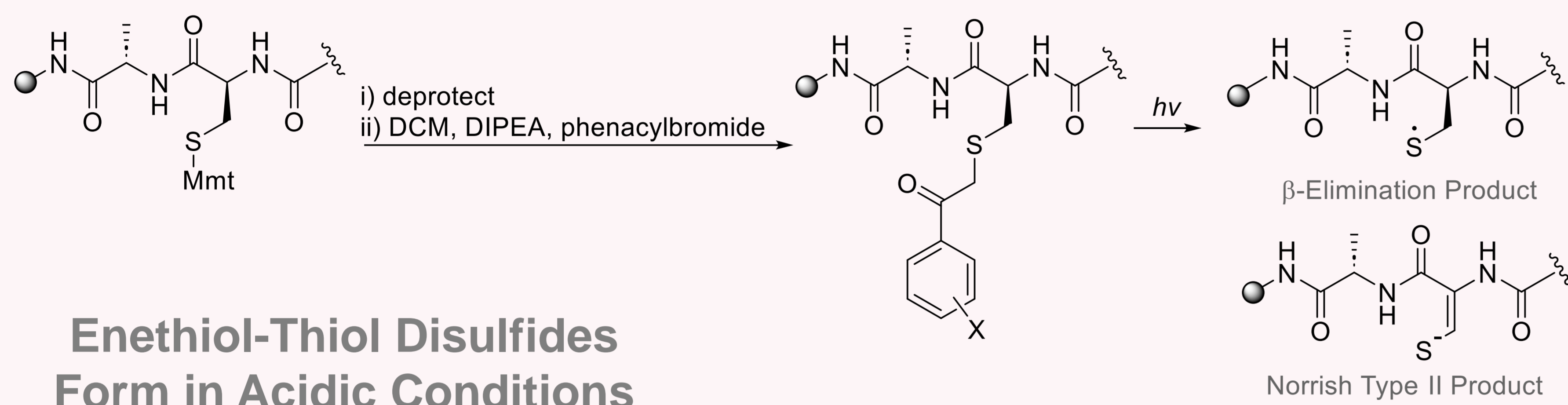
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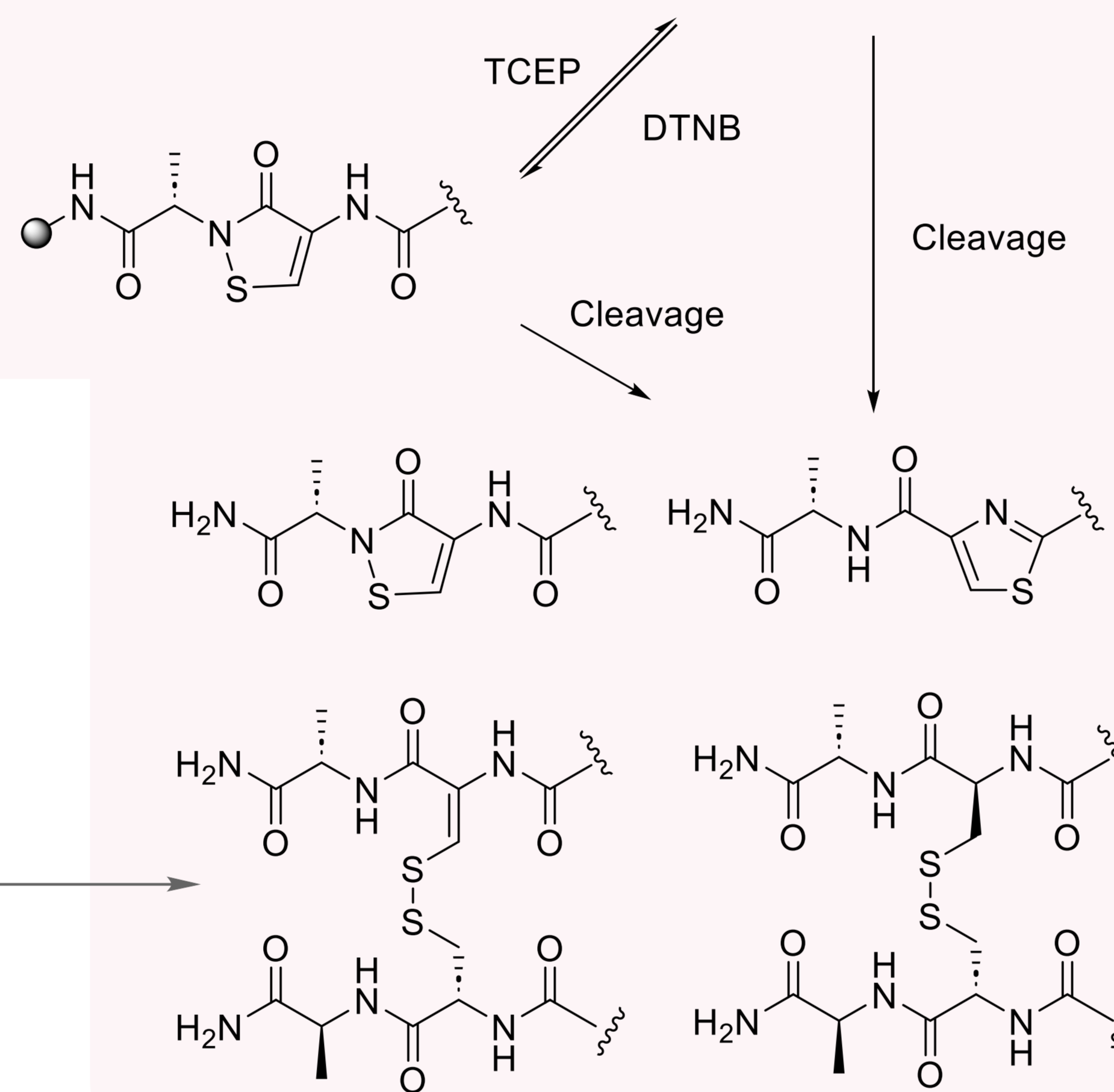
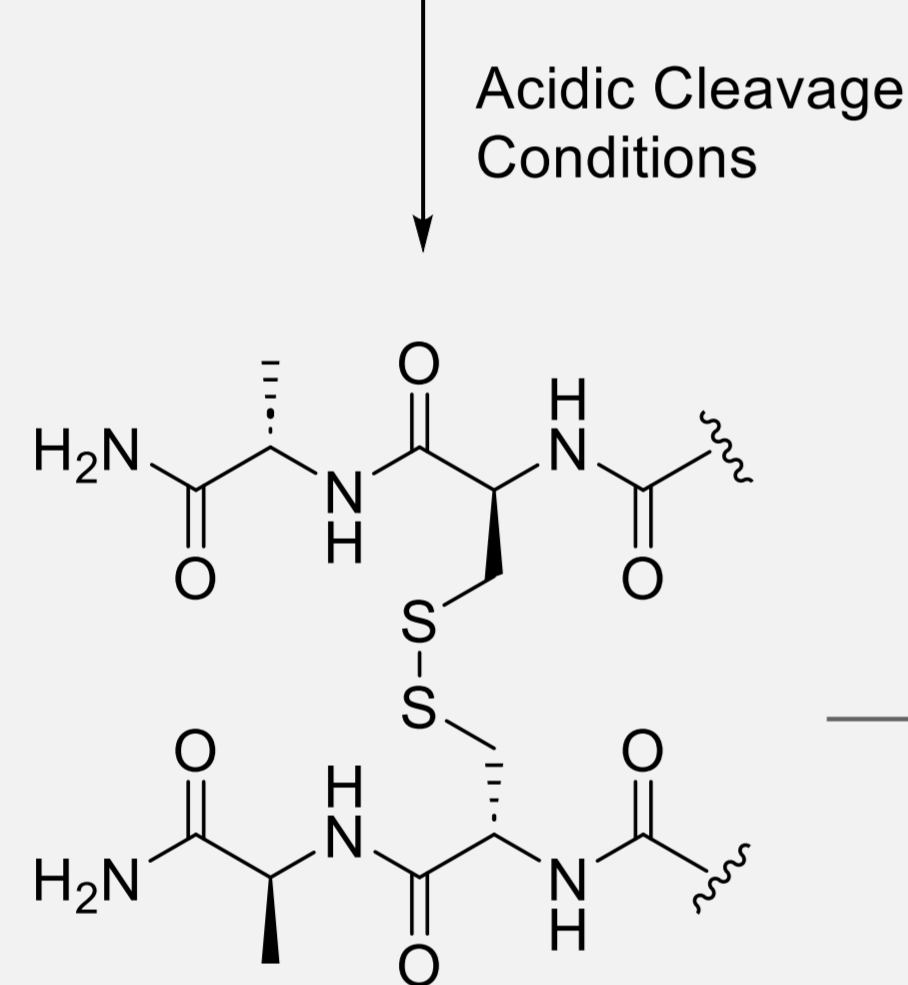
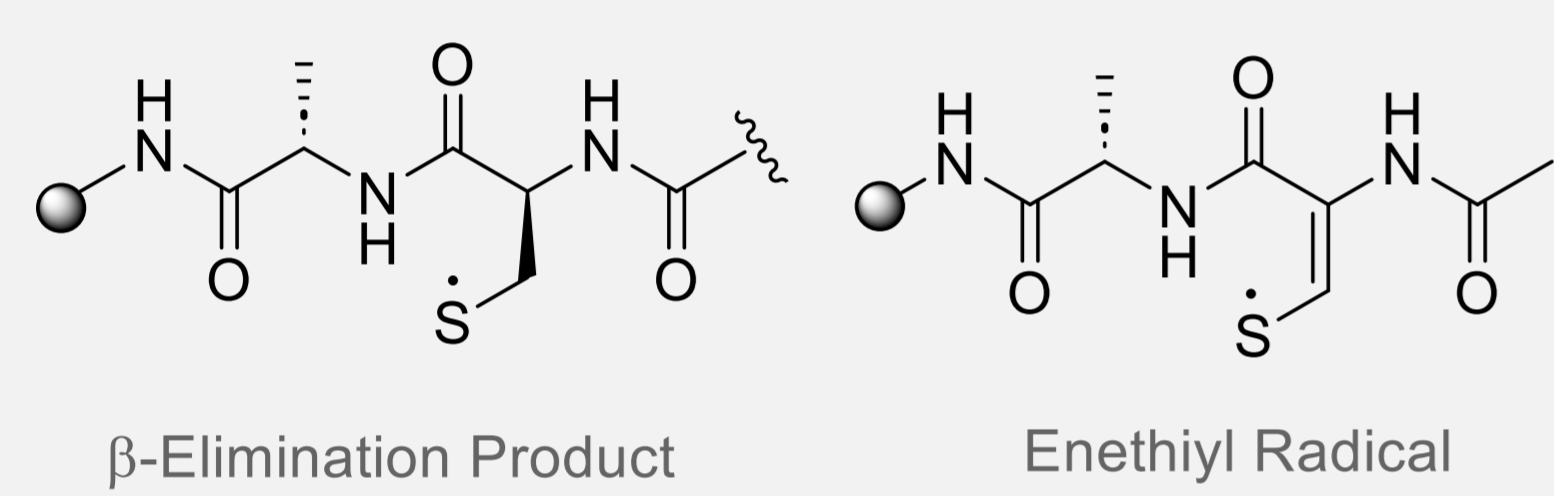
## Previous Work On Cysteine Thioaldehydes in the Myers Group<sup>1, 2</sup>



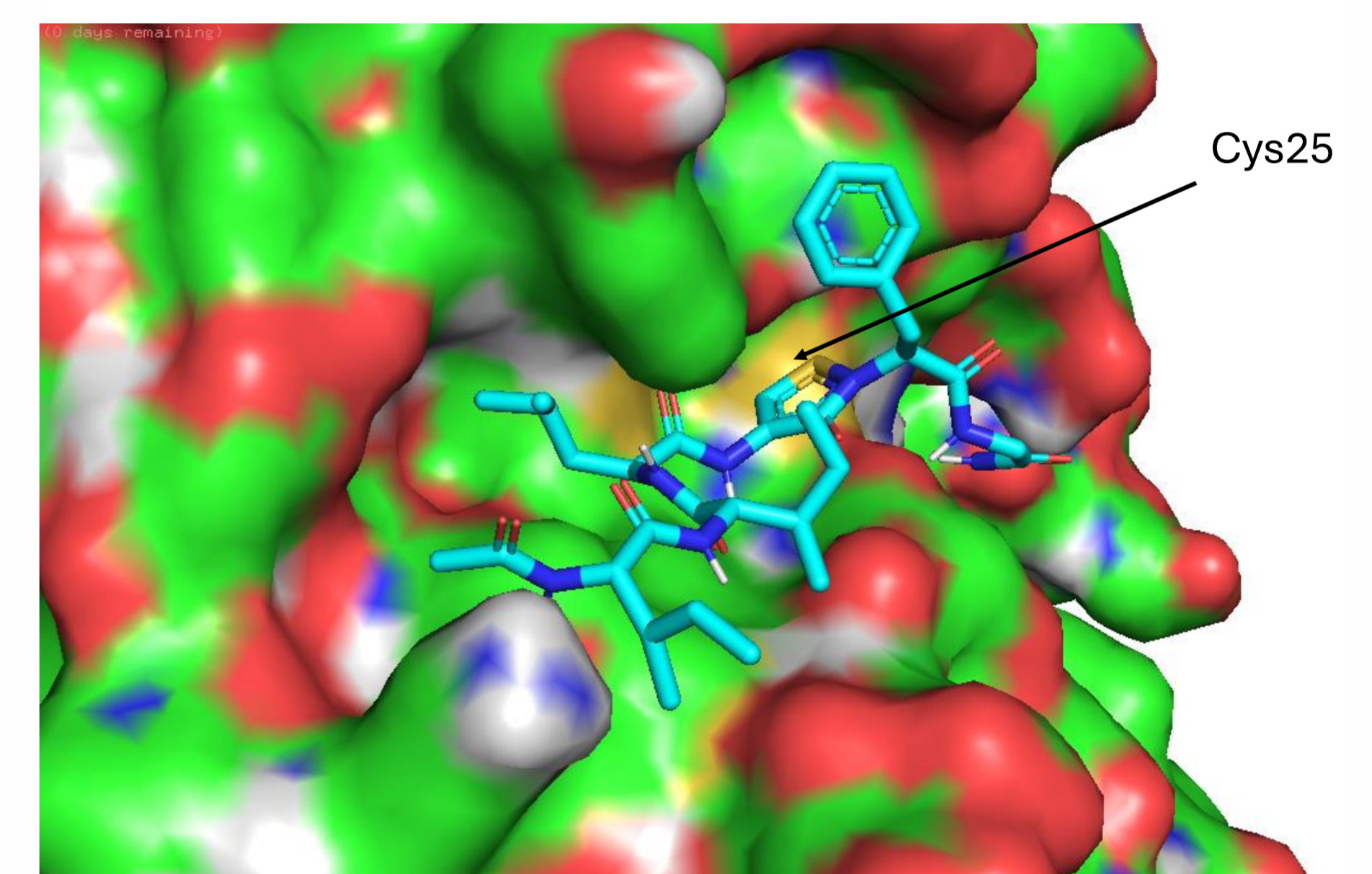
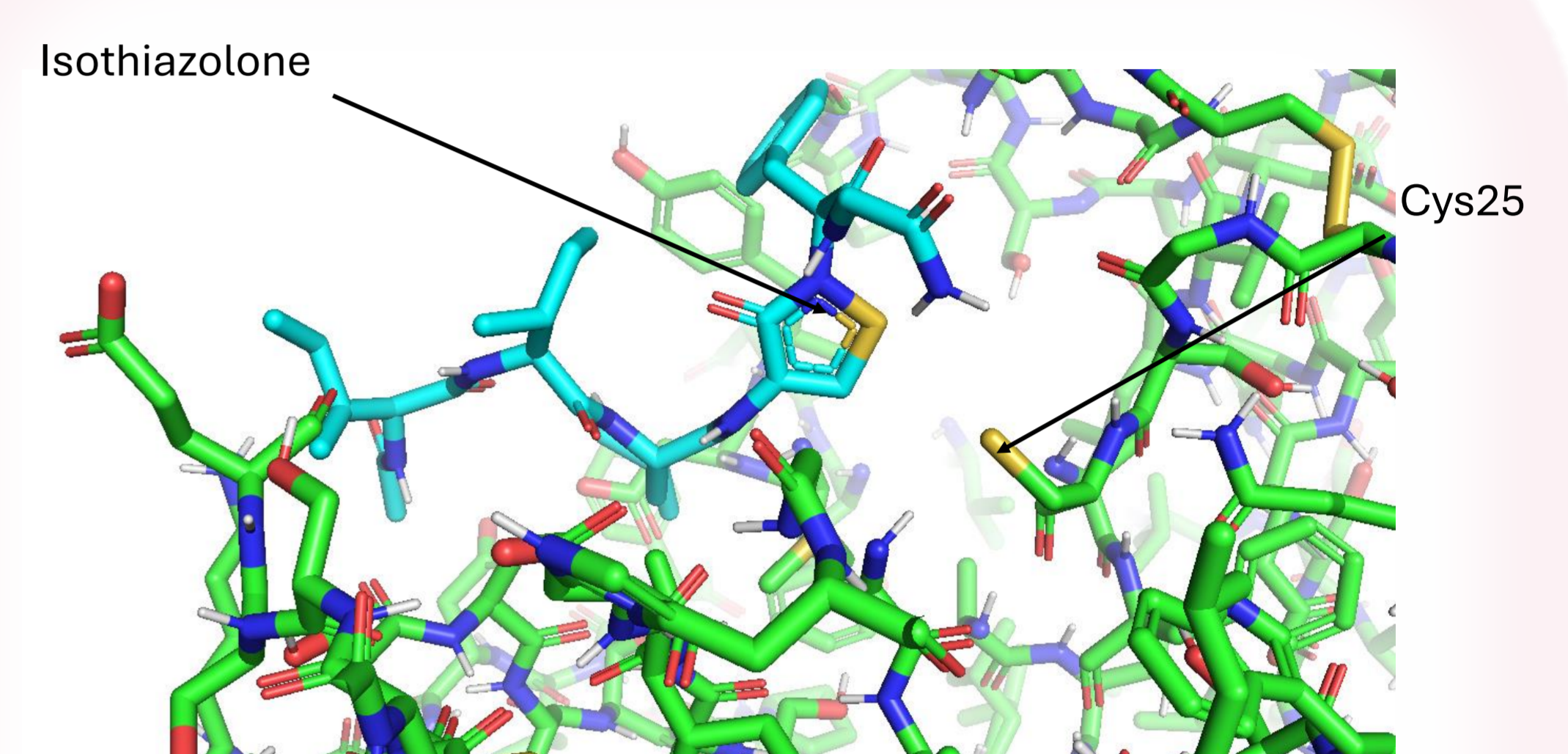
## On-Resin Synthetic Investigations of Heterocycles



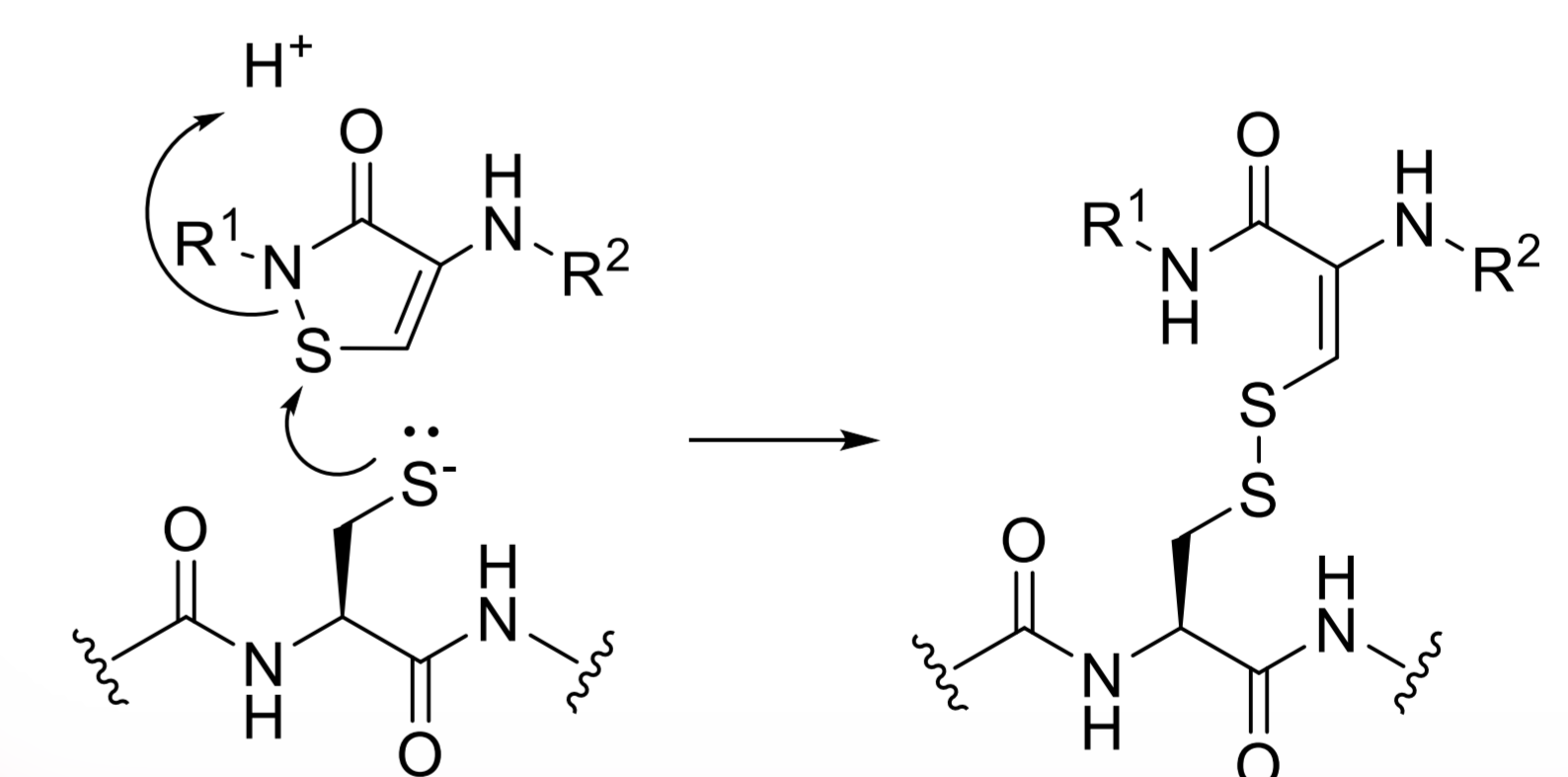
### Enethiol-Thiol Disulfides Form in Acidic Conditions



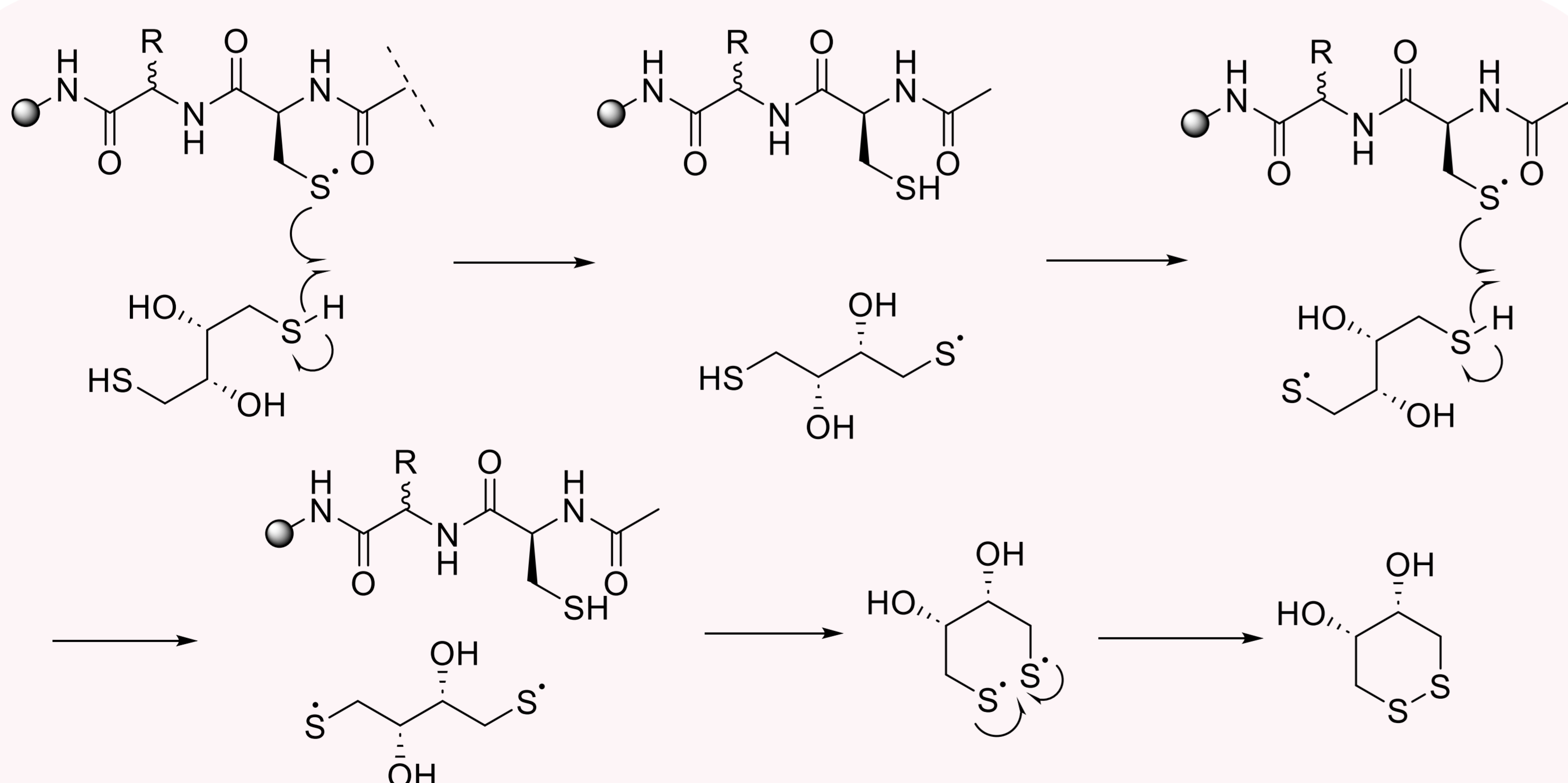
## Medical Applications of Isothiazolones<sup>3, 4</sup>



- Isothiazolones could be potential inhibitors of cysteine proteases
- The S–N bond is weak and the sulfur forms disulfides easily



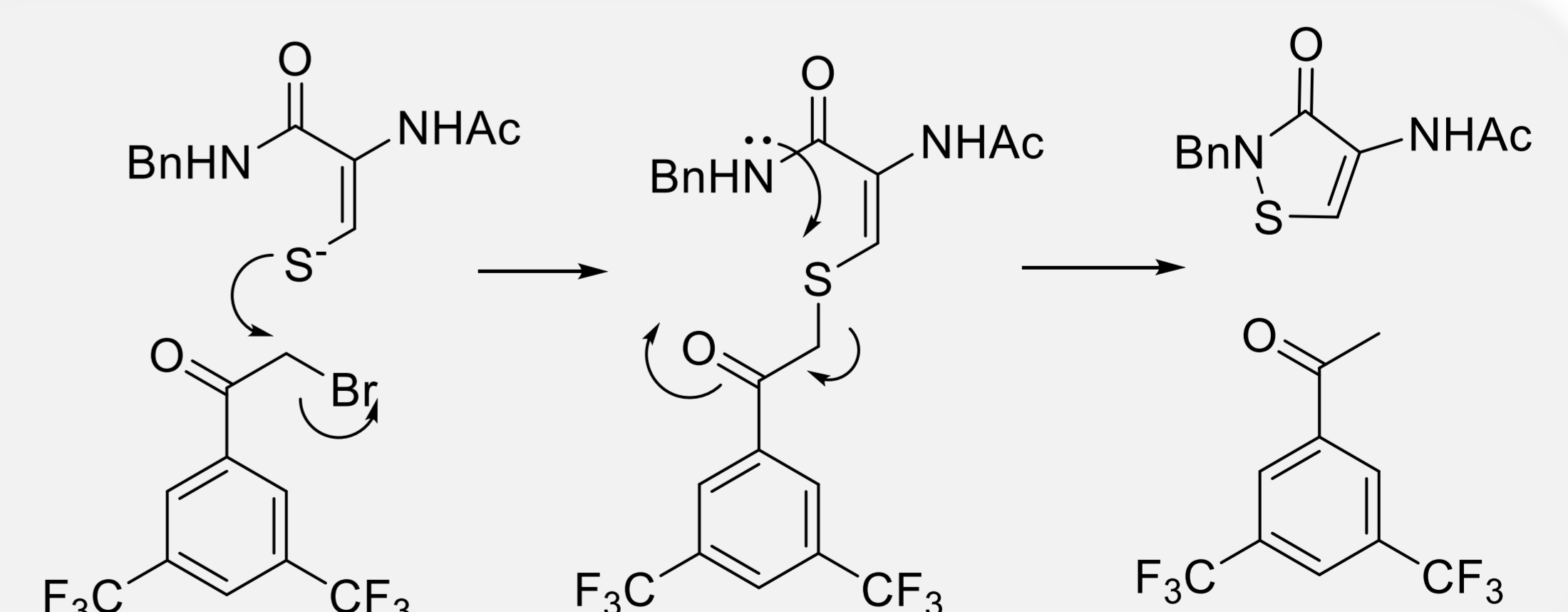
## DTT Treatment Before Cleavage Stops Disulfide Formation



## Results and Future Work

- Isothiazolone has been made on-resin but in low yield after cleavage
- Disulfides can form between enethiol and thiol radicals during cleavage
- DTT treatment prior to cleavage reduces disulfide formation and increases the amount of thiol that can react with isothiazolone
- Thiazole peptides are known bioactive molecules, and the conditions tested thus far are more suitable for their synthesis than isothiazolone containing peptides
- Thiazole has been formed in cleavage with up to 30% conversion and is less reactive to other species in solution than isothiazolone

## Enethiolate oxidation by phenacylbromides



- Enethiolate can be oxidized by DTNB or phenacylbromides

1. P. I. Clark and G. Lowe, *Journal of the Chemical Society, Chemical Communications*, 1977, 923-924

2. P. J. Wagner, *Accounts of Chemical Research*, 1971, 4, 168-177.

3. N. Hayakawa, K. Nozawa, A. Ogawa, N. Kato, K. Yoshida, K.-i. Akamatsu, M. Tsuchiya, A. Nagasaka and S. Yoshida, *Biochemistry*, 1999, 38, 11501-11507

4. Y.-H. Chen, H.-Y. Hsu, M.-T. Yeh, C.-C. Chen, C.-Y. Huang, Y.-H. Chung, Z.-F. Chang, W.-C. Kuo, N.-L. Chan and J.-H. Weng, *Journal of Medicinal Chemistry*, 2016, 59, 9906-9918.



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