

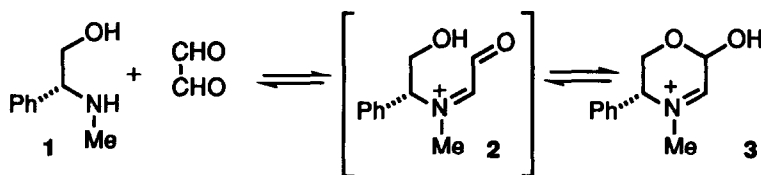
Compared Reactivity of a β -Aminothiols and a β -Aminoalcohol towards Phenylglyoxal

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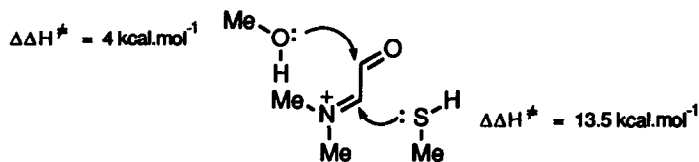
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Abstract: In agreement with a previous theoretical statement, (*R*)-*N*-methyl phenylglycinol and (*R*)-*N*-methyl phenylglycine thiol react with phenylglyoxal to give respectively six and five-membered heterocycles.

Condensation of β -amino alcohols with glyoxal leads to tetrahydrooxazines.¹ Recently we reported the results of AM1 calculations² which explain the formation of such six-membered ring on the basis of HSAB theory: the hard hydroxy nucleophile intramolecularly adds onto the carbonyl (hard acid) rather than onto the iminium ion (soft acid), both moieties being present in intermediate 2.

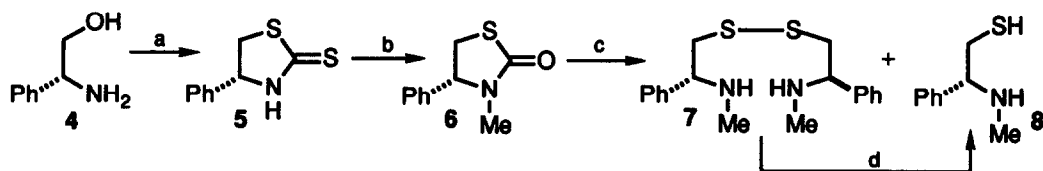


Moreover it was predicted that thiols and alcohols should exhibit opposite behaviours since these calculations showed that, as schematized below, there is a 4 kcal.mol⁻¹ activation energy difference in favor of an attack of methanol onto the oxo moiety in contrast to a 13.5 kcal.mol⁻¹ for the attack of methanethiol onto the iminium ion.



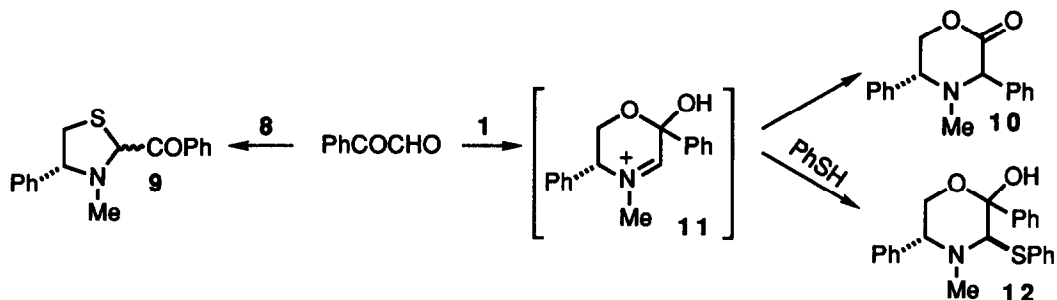
In order to check the validity of this prediction, we decided to synthesize the thio analogue of aminoalcohol 1 and to study the reactivity of this β -aminothiols in a similar condensation with an α -dicarbonyl compound. (*R*)-*N*-Methyl phenylglycine thiol 8 was obtained as shown below.

Thiazolidinethione 5 was prepared by reaction between (*R*)-phenylglycinol 4 and carbon disulfide.³ Treatment of this compound with an excess of iodomethane followed by hydrolysis yielded thiazolidinone 6 whose basic hydrolysis afforded a mixture of disulfide 7 and (*R*)-*N*-methyl phenylglycine thiol 8 in a nearly equimolar ratio. Treatment of this mixture by LiAlH₄ gave the desired thiol 8.⁴ This β -aminothiols was easily oxidized and therefore used as a crude product in the subsequent reaction.



Conditions: (a) CS₂, KOH, EtOH, reflux 15 h, 85%; (b) K₂CO₃, MeI, DMF, reflux 15 h then H₂O, reflux 1.5 h, 56%; (c) 5N NaOH, reflux 5 h, 95%; (d) LiAlH₄, Et₂O, 60%.

Reaction of aminothiols 8 with phenylglyoxal in refluxing acetonitrile produced 2-benzoylthiazolidine 9 as a mixture of two diastereomers (70:30) at C-2. Under the same experimental conditions, (*R*)-*N*-methyl phenylglycinol 1 afforded morpholinone 10.⁵ This six-membered heterocycle most probably arose from a phenyl transfer within intermediate iminium compound 11. When the condensation of aminoalcohol 1 and phenylglyoxal was performed in water solution in the presence of thiophenol, phenylthiomorpholine 12 was obtained.⁷



The present results clearly confirm the previous theoretical statement about the difference of reactivity between the oxo and the iminium moieties towards thio and hydroxy nucleophilic reagents.

References and notes

1. Agami, C.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C., *Tetrahedron*, **1990**, *46*, 7003-7010.
2. Agami, C.; Couty, F.; Hamon, L.; Puchot, C., *Tetrahedron Lett.*, **1992**, *33*, 3645-3646.
3. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E., *J. Org. Chem.*, **1986**, *51*, 2391-2393.
4. All compounds gave satisfactory (¹H and ¹³C NMR) spectral data and elemental analysis except for aminothiols 8 whose purification was unsuccessful.
5. In agreement with an earlier work⁶, we observed that ephedrine, i. e. a β-aminoalcohol having a secondary hydroxyl moiety, reacts with phenylglyoxal to afford the corresponding 2-benzoyloxazolidine.
6. Vigneron, J. P., unpublished results.
7. Products 10 and 12 were obtained as single diastereomers but their relative configurations were not determined.