

Ab initio evaluation of metalated 3-halo-1-azaallylic anions as synthetic building blocks

Bart De Sterck,[†] Veronique Van Speybroeck,[†] Guido Verniest[‡] Sven Mangelinckx,[‡]
Norbert De Kimpe,[‡] Michel Waroquier[†]

[†]Center for Molecular Modeling, Ghent University

[‡]Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University

α -Heteroatom-substituted carbanions stabilized by an electron-withdrawing group (acyl, alkoxy-carbonyl, sulfonyl, sulfinyl, cyano, carbamoyl) have been used intensively as synthetic building blocks for the production of a great variety of azaheterocyclic compounds.[1] However, one combination appears to be unsuccessful, when a halogen and an acyl group are combined. This is due to the instability and non-selective reactivity of β -haloenolates **2** derived thereof (Figure 1).[2]

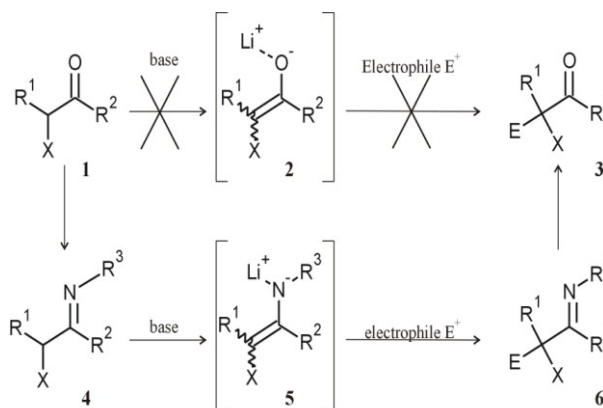


Figure 1. Conversion of α -haloketones **1** to α -haloimines **4** and further to functionalized imines **6** and ketones **3**.

A convenient way to overcome these problems is the conversion of α -haloketones **1** towards the corresponding less reactive α -haloimines **4**. After deprotonation of these imines, the 3-halo-1-azaallylic anions **5** are formed.[3] It is seen that the presence of a halogen (X) results in a well-defined absolute minimum configuration of the 3-halo-1-azaallylic anions. In this way, α -functionalized α -haloimines **6** and α -functionalized α -haloketones **3** can be prepared via subsequent reaction of these 3-halo-1-azaallylic anions with electrophiles.[2]

An example of such an electrophile is benzaldehyde. Experimental as well as theoretical work has been done on the addition of benzaldehyde to (mostly boron) enolates and aza-enolates.[4] The effect of a halogen on the reactivity and product distribution has not been examined theoretically yet. The presence of the halogen, however, has great potential for the production of biologically active molecules. It seems that the 3-halo-1-azaallylic anions are very suitable building blocks for the production of azaheterocyclic compounds which exhibit biological activity.

- [1] Krief, A., *Tetrahedron* 36 (1980) 2531.
 [2] Mangelinckx, S., Giubellina, N. and De Kimpe, N., *Chem. Rev.* 104 (2004) 2353.
 [3] Knorr, R. and Low, P., *J. Am. Chem. Soc.* 102 (1980) 3241.
 [4] Bernardi, A., Gennari, C., Goodman, J.M., Leue, V. and Paterson I. *Tetrahedron* 51 (1995) 4853.

E-mail: bart.desterck@ugent.be

www: <http://molmod.ugent.be/>