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Indium and Zinc Mediated One-Atom Carbocycle Enlargement In Water

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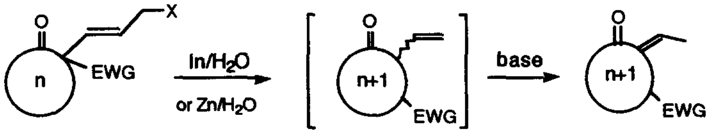
(Dedicated to Professor David N. Harpp on the occasion of his 60's birthday)

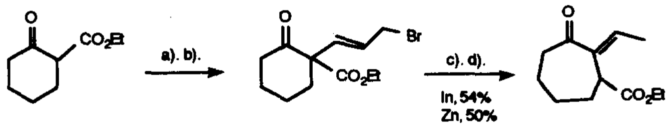
Summary. *Six-, seven-, eight-membered rings are enlarged by one carbon-atom into seven-, eight- and nine-membered ring derivatives respectively, via indium or zinc mediated reactions in aqueous medium.*

Medium and largesize rings are the structural core of a large number of biologically important natural products.[1] Among the various methods for medium and large ring synthesis,[2] ring expansion provides the chemist with a unique method of ring formation, inasmuch as the usually disfavored entropy encountered in medium and large size ring formations can be avoided.[3] Recently, we reported[4] a novel ring enlargment methodology where carbocycles are expanded by two carbons through the indium-mediated Barbier-type reaction in aqueous medium.[5] Here we report a one atom carbocycle ring expansion that may be mediated by either indium or zinc (Eq. 1).



(1)

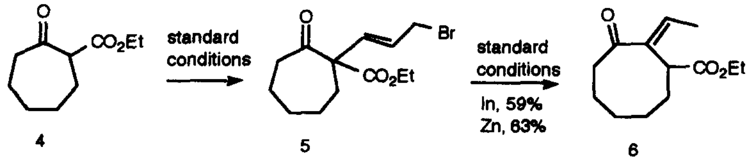
In the sequence below (Eq. 2), allylation of ethyl 2-oxo-1-cyclohexanecarboxylate (**1**) in DMF followed by NBS bromination yielded the allyl bromide **2**. Stirring the bromide with indium powder in water for 24h resulted in the recovery of the starting material. However, when the reaction was performed in acidic media, the desired product was obtained. It was found that adjusting the acidity level of the aqueous solution was critical for the success of this type of reaction; for this particular reaction, it was discovered that by using a combination of 0.025N HCl/THF (10:1) as the reaction medium, the bromide **2** was successfully expanded to a diastereomeric mixture of seven-membered ring compounds with indium (20hr, r.t.). Following treatment of the reaction mixture with DBU in THF (2hr, r.t.), the ethylendienecycloheptane compound **3** was obtained in 54% after purification by column chromatography on silica gel (eluent: ethyl acetate/hexane = 1:10). By using a similar sequence of transformations, seven- and eight-membered ring derivatives are expanded into eight- and nine-membered ring compounds **6**, and **9**.



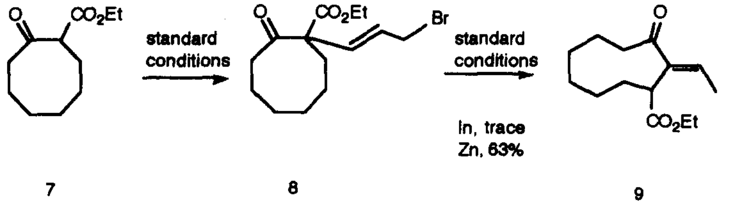
1 2 3

(2)

Conditiones: a). NaH/Allyl bromide/DMF/r.t., 15h; b). NBS/CCl$_4$/reflux, 3h; c). In or Zn /0.025 N aq. HCl-THF(10:1)/r.t., 20h; d). DBU/THF/r.t., 2h.



(3)



(4)

It would appear that zinc facilitates more consistent results; the yields of the indium mediated reactions seem to be directly proportional to the length of time that the indium remains in its powdered form during the course of the reaction. In the case of Eq. 4, for example, it was difficult to prevent the congealing of the indium powder into solid lump of metal early in the reaction, resulting in a lower yield. Zinc, however, does not appear to be affected in this way, giving higher and more consistent yields. Potential methods for surmounting this problem are currently being investigated. This transformation presents a room temperature, aqueous alternative to the tri-n-butyltin hydride ring expansion, normally conducted in refluing organic media such as benzene.[6]

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