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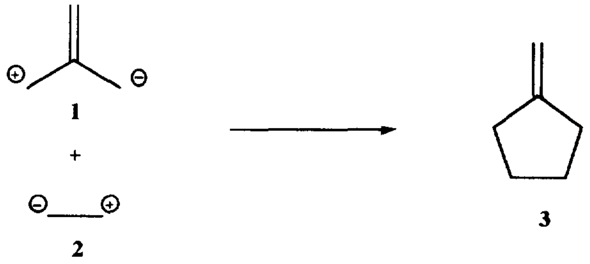
NOVEL [3+2] ANNULATION VIA A TRIMETHYLENEMETHANE ZWITTERION EQUIVALENT IN WATER

*Yue-Qi Lu and Chao-Jun Li**
Department of Chemistry, Tulane University, New Orleans, LA 70118, USA

Abstract: *Sequential nucleophilic and electrophilic alkylations of 1,3-dicarbonyl compounds with a trimethylenemethane zwitterion equivalent lead to a novel [3+2] annulation. The carbonyl alkylation was carried out via a metal mediated allylation reaction in water.*

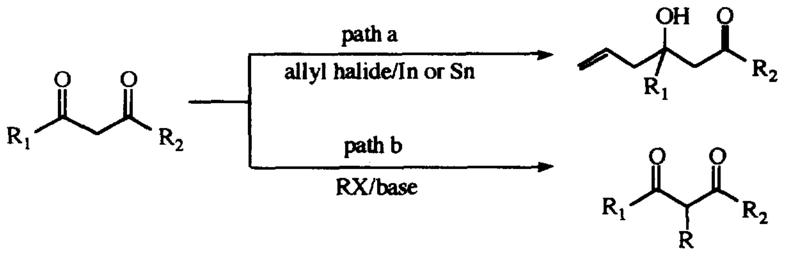
Cyclopentanoids constitute one of the most common structural features for many natural and non-natural products.[1] Many research efforts have been devoted to their formations.[2] Among the most useful methods are the [3+2] cyclization approaches. Very often these cyclizations are carried out through transition metal catalysis.[3] We report herein a new [3+2] annulation methodology involving a reaction between a trimethylenemethane zwitterion equivalent (**1**) and a 1,2-zwitterion equivalent (**2**) (Eq. 1). The cyclization was carried out via the indium mediated allylation reaction in water.[4]



(Eq. 1)

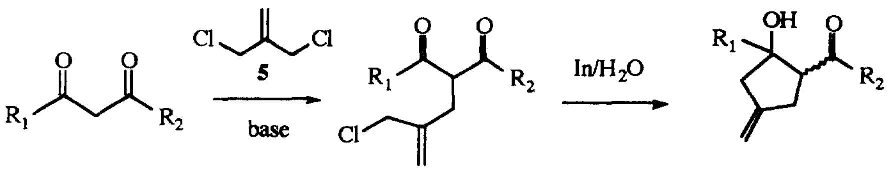
Recently, we reported a simple and efficient approach towards the carbonyl alkylation of 1,3-dicarbonyl compounds.[5] A variety of carbonyl compounds have been nucleophilically allylated in this way. The reaction is based on a Barbier-type reaction in aqueous media by using either tin or indium as the metal mediator (Eq. 2, path a).[6] In this reaction, the disfavored effect of enolization of 1,3-dicarbonyl compounds which often competes with the carbonyl alkylation has been prevented.

On the other hand, 1,3-dicarbonyl compounds are excellent nucleophilies for organic transformations. The electrophilic alkylation of 1,3-dicarbonyl compounds and related compounds whereby stabilized carbanions react with an alkyl halide to give the corresponding alkylation products (Eq 1, path b) constitutes one of the most useful methods for carbon-carbon bond formation.[7] These dicarbonyl compounds have also been used as nucleophiles in a variety of transition-metal catalyzed alkylation reactions[8], in Michael addition reactions[9] and in condensation reactions.[10]



(Eq. 2)

By combining their nucleophilic and electrophilic properties, 1,3-dicarbonyl compounds can react with 3-chloro-2-chloromethylpropene and indium sequentially, which ultimately leads to a convenient annulation method for 5-membered carbon rings (Eq. 3). In this reaction, 2-chloro-2-chloromethylpropene (**5**) serves as a useful trimethylenemethane zwitterion equivalent (**1**), while 1,3-dicarbonyl compound (**4**) serves as the 1,2-zwitterion equivalent (**2**).



(Eq. 3)

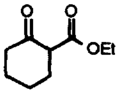
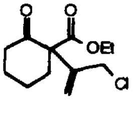
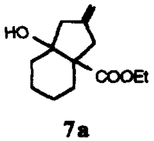
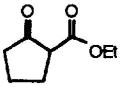
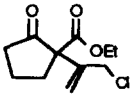
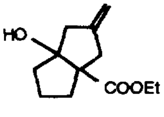
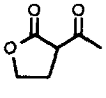
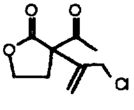
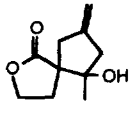
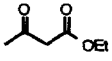
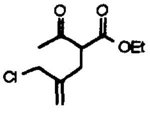
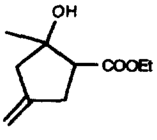
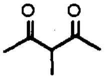
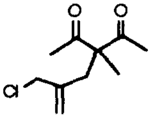
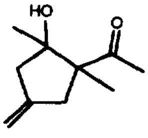
4 **6** **7**

Thus, reaction of 1,3-dicarbonyl compound **4d** with 2-chloro-2-chloromethylpropene under basic conditions lead to primarily the monoalkylation product **6d**. Subsequent reaction of this intermediate compound with indium metal in water lead to the cyclized product **7d** in excellent yields. Other 1,3-dicarbonyl compounds react similarly. Some results have been summarized and are provided in Table 1. The presence of exocyclic methylene group in the products provides a handle for further structural elaborations.

A typical procedure for preparing the intermediate: to a suspension of NaH (80 mg, 60% w/w in mineral oil, 2 mmol) in 10 ml DMF was added ethyl acetoacetate (**4d**, 260 mg, 2 mmol). The reaction mixture was stirred for 30 min under nitrogen and subsequently transferred to a solution of methallyl dichloride (375 mg, 3 mmol) in 10 ml DMF. After stirred for 3 hours, the reaction mixture was quenched with 1N HCl aqueous solution, and extracted with ether (4x20 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. The product, ethyl 2-acetyl-4-chloromethyl-4-pentenoate (**6d**, 262 mg, yield 60 %), was isolated by flash chromatography on silica gel (eluent: hexane/EtOAc=7/1).

A typical procedure for the cyclization: to a suspension of ethyl 2-acetyl-4-chloromethyl-4-pentenoate (262 mg, 1.2 mmol) in 10 ml 0.1N HCl aqueous solution was added indium powder (**6d**, 228 mg, 2 mmol). The reaction mixture was stirred vigorously for 12 hours, diluted with 1N NH_4Cl, and extracted with ether (4x10 ml). The combined ether solution was dried over $MgSO_4$ and concentrated. The cyclization product, ethyl 2-hydroxyl-2-methyl-4-methylenecyclopentylcarboxylate (**7d**, 203 mg, yield 92 %), was isolated by flash chromatography on silica gel (eluent: hexane/EtOAc=7/1).

Table I. Novel [3+2] annulation in water leads to cyclopentanoids

Entry	Substrate(1)	Product(6)	Yield(%)	Product(7)	Yield(%)^a
1	 **4a**	 **6a**	65	 **7a**	98
2	 **4b**	 **6b**	63	 **7b**	98
3	 **4c**	 **6c**	60	 **7c**	quant.
4	 **4d**	 **6d**	60	 **7d**	92
5	 **4e**	 **6e**	60	 **7e**	90

For entries 1-3, cyclizations were carried out in water; for entries 4 and 5, cyclizations were carried out in 0.1N HCl aqueous solution. A single diastereomer was obtained for entries 1 and 2; a mixture of diastereomers was obtained for entries 3-5.

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