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Abnormal Nucleophilic Reaction of Ethyl Crotonate: An Easy Way to Form Novel Imidazo[1,5-a] pyridine derivatives

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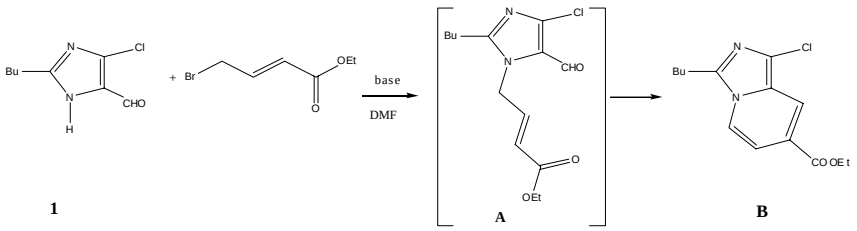
Abstract: An abnormal intramolecular nucleophilic reaction of α-carbon of α, β-unsaturated ester was discovered and the reaction makes it very easy to form imidazo[1,5-a]pyridine derivatives. The mechanism of the reaction was discussed.

Keywords: Nucleophilic reaction, α, β-unsaturated ester, imidazo[1,5-a]pyridine derivatives, mechanism.

It is well known that β-carbon of α, β-unsaturated ester has an eletrophilic property and subject to nucleophilic attack. This kind of reaction called "conjugated addition" or "Michael addition"[1,2]. The α-carbon of unsaturated ester is rarely considered by chemists to react with electrophilic groups. In our work of making new Losartan[3] derivatives, we found an abnormal reaction of the α-carbon of α, β-unsaturated ester.

Our original purpose was making compound **A** by reaction of **1** and ethyl 4-bromocrotonate. Unexpectedly, we obtained compound **B**.



1 **A** **B**

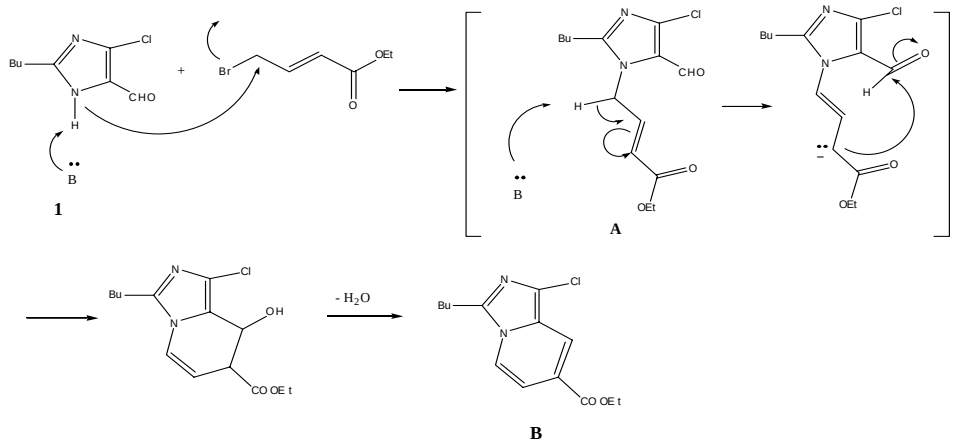
In the literature, the only way to form imidazo[1,5-a]pyridine ring was by the phase transfer catalyzed reaction of 2-(aminomethyl)pyridine with $CHCl_3$ and alkaline hydroxide[4]. The quaternary salts of imidazo[1,5-a]pyridine were used as the hypoglycemic agents[5,6].

Our reaction can be used to make imidazo[1,5-a]pyridine derivatives with variable substituents on them and they will be very useful in bio-active studies.

The reaction was done as follows: To equal mole of 2-butyl-4-chloro-5-imidazol-aldehyde and ethyl 4-bromocrotonate in DMF, 1.2 equal mole of K_2CO_3 was added. After stirring over night at room temperature, the mixture was

poured into excess water and extracted with CH_2Cl_2. The organic layer was separated and washed with water and dried over Na_2SO_4, the product **B** was purified by column chromatography on silica gel. The yield was about 80-90%.

In order to understand the results, different reactions were done. The imidazol-aldehyde **1** reacted with allyl bromide in the same condition, the N_1-allyl substituted imidazolaldehyde was obtained in 90% yield; the product 2-butyl-1-allyl-4-chloro-5-imidazolaldehyde does not cyclize. While **1** was added with ethyl 4-bromocrotonate in DMF without base, no reaction occurred. But after the base (K_2CO_3) was added, the reaction went immediately to form the compound **B**. The reaction mechanism can be proposed as follows: the base attacks the proton on the N_1 of the imidazole ring first and N_1 atom in turn substitutes bromo from ethyl 4-bromocrotonate and forms the intermediate **A**, then base again attacks the proton on γ -carbon and anion carbon is formed own to the conjugated effect of the ester. For the conjugated and structural favorable, the anion α -carbon attacks the carbonyl group to form the six member ring and the dehydration is followed and a new bicyclic compound, imidazo[1,5-a]pyridine derivatives **B** are formed.



The structure of the compound **B** (oily) was confirmed by ^{1}HNMR and MS. ^{1}HNMR ($CDCl_3$, TMS): δ =0.9(t,3H);1.4(m,5H);1.8(m,2H);2.9(t,2H);4.2(q,2H);7.0(dd,1H);7.4 (dd,1H);8.0(d,1H). MS: m/z=280(M^+,40%). Their antihypertensive and hypoglycemic activities are undertaking.

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