# Accepted Manuscript


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PII: S1001-8417(18)30003-2
DOI: https://doi.org/10.1016/j.cclet.2018.01.003
Reference: CCLET 4393

To appear in: *Chinese Chemical Letters*

Please cite this article as: Chang Xiao, Song-Lin Zhang, Mechanism for acetic acid-catalyzed ester aminolysis, Chinese Chemical Letters https://doi.org/10.1016/j.cclet.2018.01.003

Communication

# Mechanism for acetic acid-catalyzed ester aminolysis

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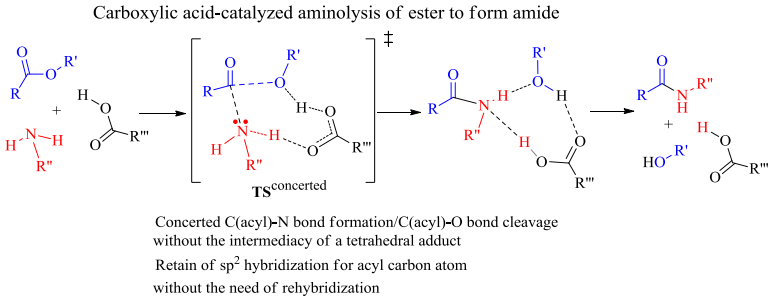
## Graphical Abstract




A computational study is described to elucidate the mechanism for acetic acid-catalyzed ester aminolysis to produce amides. A concerted acyl substitution mechanism is proposed to involve concurrent acyl-O bond cleavage and acyl-N bond formation where acetic acid acts as a bifunctional catalyst connecting to both the alkoxide and the amino moieties. This mechanism does not involve the intermediacy of a tetraheral adduct nor the rehybridization of acyl carbon, in sharp contrast to classic stepwise acyl substitution mechanism.

ARTICLE INFO

*Article history:*
Received 16 November 2017
Received in revised form 20 December 2017
Accepted 27 December 2017
Available online

*Keywords:*
Amide bond formation
Aminolysis
Mechanism
Ester
Concerted acyl substitution
Acid catalyzed amidation

ABSTRACT

This paper reports a computational study elucidating reaction mechanism for amide bond formation from esters and amines catalyzed by acetic acid. Two optional mechanisms (namely, classic stepwise and concerted acyl substitution mechanisms) have been studied. Calculation results establish the reaction energy profiles of both mechanisms and locate all the intermediates and transition states in both catalytic cycles. Our results propose that the concerted acyl substitution mechanism may be more likely wherein the formation of C-N bond and the cleavage of C-O bond occur concurrently without the need of rehybridization of the carbonyl carbon. This is also consistent with the fact that no significant racemization/epimerization were observed in the amide products when asymmetric esters and/or amines were used as the reactants, because concerted acyl substitution mechanism precludes the intermediacy of tetrahedral adducts and the accompanying generation/elimination of new chiral centers. Further discussion implies that the concerted acyl substitution mechanism may widely occur in related amidation reactions in the presence of different types of coupling reagents.

Due to the ready generation of ammonium carboxylate salts, amide bond formation by direct condensation of carboxylic acids and amines is challenging and often needs high temperatures or the presence of stoichiometric amounts of sacrificing coupling reagents [1,2]. To solve this problem, great efforts have been made to construct amide bond from coupling of activated acyl and/or amino reagents [3]. Among the diverse strategies, aminolysis of active esters by amines is one attractive practical method, which is apparently a nucleophilic carbonyl substitution reaction with the replacement of an alkoxide by an amino group [4].

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