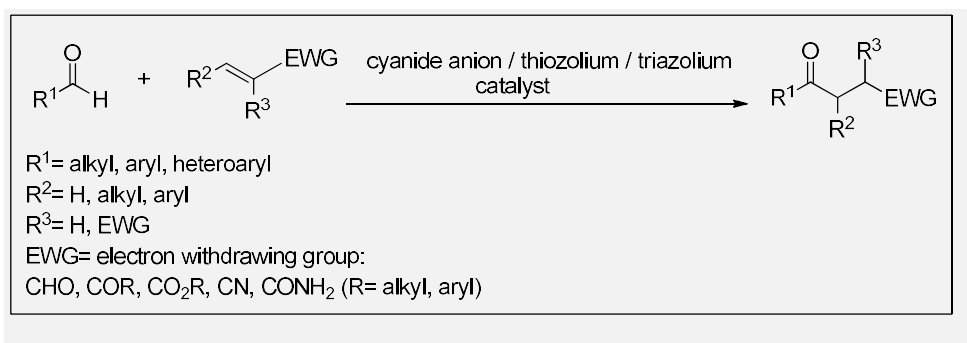


Stetter Reaction: A Novel Source to the Synthetic Chemistry

Dandamudi V. Lenin*

Abstract: Carbon-carbon bond forming reaction is one of the most fundamental reactions in synthetic organic chemistry. Numerous C-C bond forming reactions such as Aldol reaction, Suzuki coupling, Grignard reaction, Baylis-Hillman reaction, Heck reaction, Diels-alder reaction and Wittig reaction *etc.* have been well-known. New approaches for expansion of carbon-carbon bonds have been nonstop challenging and attractive endeavour to synthetic organic chemists. The Stetter reaction is added important carbon-carbon bond forming reaction which is increasing quickly in recent years.

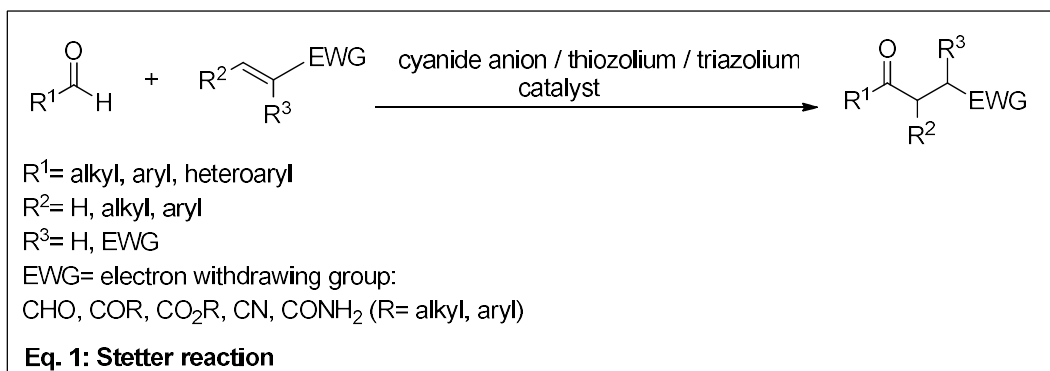


1. Introduction of the reaction

Carbon-carbon bond forming reaction is one of the most important reactions in synthetic organic chemistry. Many C-C bond forming reactions such as Aldol reaction,¹ Suzuki coupling,² Grignard reaction,³ Baylis-Hillman reaction,^{4,5} Heck reaction,⁶ Diels-alder reaction⁷ and Wittig reaction⁸ *etc.* have been well-known. New approaches for expansion of carbon-carbon bonds have been nonstop challenging and attractive endeavour to synthetic organic chemists. New strategies for development of carbon-carbon bonds have been nonstop

* School of Chemical Sciences, Central University of Gujarat, Gandhinagar, India.

challenges to synthetic organic chemists. The Stetter reaction⁹⁻²¹ is added important carbon-carbon bond forming reaction which is increasing quickly in recent years.



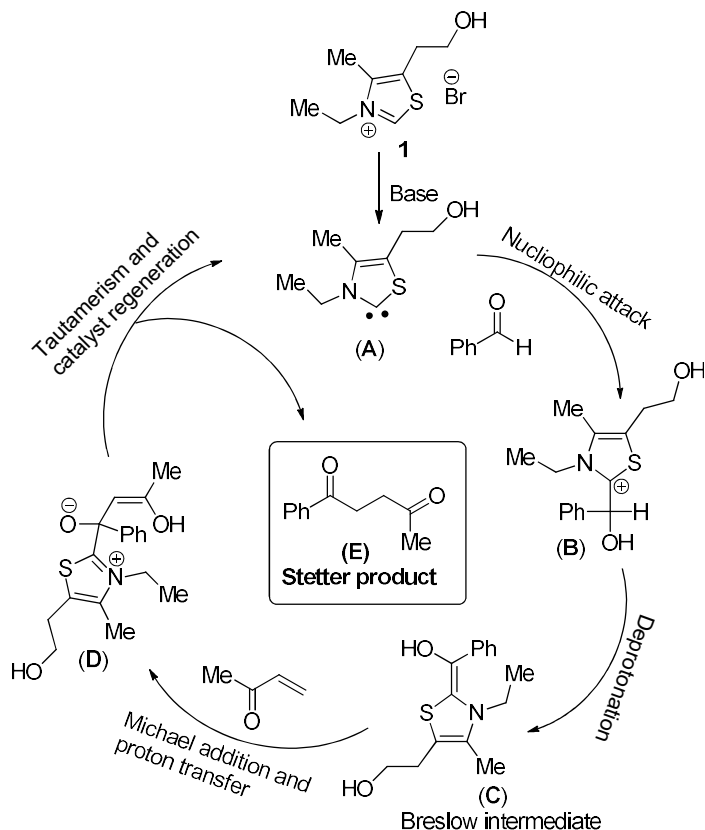
2. Origin of the reaction

In 1973, Hermann Stetter²²⁻²⁶ reported the conjugate addition of aldehydes to α , β -unsaturated compounds, which yield 1,4-dicarbonyl compounds in the presence of cyanide anion or thiazolium salt as a catalyst. Since then 1,4 addition of aldehydes to Michael acceptors in the presence of cyanide anion or thiazolium or triazolium salt catalyst has been known as Stetter reaction (eq 1). This inspiring reaction possess atom economy, stereo and regio-selectivity which are the most essential requirements for the development of an efficient synthetic reaction. It enables a new catalytic pathway for the synthesis of various 1, 4-bifunctional molecules such as diketones, ketoesters and ketonitriles *etc.* can be catalyzed by a broad range of thiazolium and triazolium salts which make this reaction more attractive in the synthetic organic chemistry. A variety of aliphatic and aromatic aldehydes into 1,4-dicarbonyl compounds with various Michael acceptors. Many electrophiles, Michael acceptors and catalysts has been employed effectively.

3. Mechanism of the reaction

The reaction mechanism²⁷⁻²⁹ is the conversion of the carbonyl group from an electrophile to a nucleophile in an umpolung process is the key step. The mechanism is well-defined for the reaction among methyl vinyl ketone (MVK) and benzaldehyde where 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium bromide (**1**) used as a catalyst (Scheme 1). It is assumed that in the process, thiazolium salt **1**, undertake deprotonation at its most acidic position to form thiazoline-2-ylidene **A**, which, then go complete nucleophilic addition with benzaldehyde to produce thiazolium adduct **B**. The thiazolium adduct **B** upon deprotonation procedures an

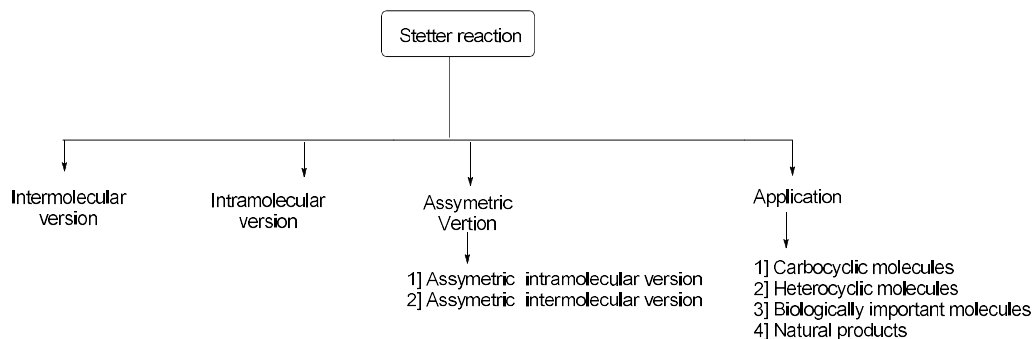
enaminol-type intermediate **C** (Breslow intermediate) which acts as a nucleophilic acylation reagent (**C**). It reacts with MVK (Michael acceptor) to form zwitterionic enolate **D**. The tautomeric rearrangement of **D** generates the Stetter product **E** and regenerate the thiazoline-2-ylidene **A**.



Scheme 1 Mechanism of Stetter reaction catalyzed by thiazolium catalyst

4. Applications of the reaction

Due to the presence of various functional groups in the proximity, applications of the Stetter adducts become significant substrates. Synthesis of numerous molecular frameworks like carbocycles, heterocycles, medicinally important compounds and natural products are well documented in literature. Great number of publications³⁰⁻³³ in literature on this reaction is the clear indicator of the importance of this reaction. This reaction has also been employed in intramolecular version, asymmetric version.^{34,35}



5. Conclusions and future of the reaction

This article demonstrates the origin and development. Though there is growth in designing and synthesizing various chiral catalysts, in the asymmetric Stetter reaction it is still important to see more and more effective chiral catalysts. Hence, there are challenges for organic chemists to develop the Stetter reaction in all kind of the essential components *i.e* electrophiles, Micheal acceptors and catalysts.

7. Acknowledgments

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