Meyer-Schuster Rearrangement—Convenient Synthesis of α,β -Unsaturated α -Iodinated Aldehydes and Ketones

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Abstract The Meyer-Schuster rearrangement reaction has been known for almost a hundred years. It has been used to prepare unsaturated aldehydes, ketones, and even esters from propargyl alcohols. Thirty years ago, the same reaction was found to produce also α -halogenated aldehydes and ketones under suitable conditions. In the last thirty years, several methods have been developed utilizing the Meyer-Schuster rearrangement in the synthesis of halogenated building blocks for use in synthetic chemistry. In this perspective, we describe the progress in the field.

Keywords Meyer-Schuster rearrangement, unsaturated α -iodo enones, propargyl alcohol, Rupe rearrangement

In synthetic chemistry, α,β -unsaturated α -halogenated aldehydes and ketones are useful building blocks for several families of compounds. For example, they are used in the stereoselective vinylogous Mukaiyama aldol reaction,^[1] in the synthesis of heterocycles like triazides,^[1] and in cross-coupling of iodoenones and stannanes to form bisenones.^[2]

One reaction to prepare α,β -unsaturated α -iodo aldehydes and ketones is the Meyer-Schuster rearrangement published first in 1922 by Kurt Heinrich Meyer and Kurt Schuster.^[3] In the reaction, a propargyl alcohol undergoes a rearrangement reaction forming an α,β -unsaturated keto-compound. Depending on the position of triple-bond, either an aldehyde or a ketone is formed (Figure 1). Several Meyer-Schuster reactions have been described in two recently published review articles.^[4,5]

Acid catalyzed reaction by Meyer & Schuster in 1922^[3]

HI/O₂ based reaction by Chen & Wang in 2007^[7]

I₂ promoted reaction by Zhu et al. 2015^[13]

Figure 1 Meyer-Schuster rearrangement of propargyl alcohols.

Nowadays, several modifications to the Meyer-Schuster rearrangement have been developed and some of the modifications have been utilized for the preparation of α -halogenated aldehydes and ketones.

In the first published Meyer-Schuster reaction to prepare

α,β -unsaturated α -iodo aldehydes from α -ynols, Antonioletti *et al.*^[6] used pyridium dichromate and iodine for the transformation. In addition, molecular oxygen (O₂) has been used to assist in the rearrangement.^[7] In one of the first metal catalyzed Meyer-Schuster rearrangements for the preparation of linear α -iodoenones from propargylic acetates, Au(PPh₃)NTf₂ was used to catalyze the reaction.^[8] In 2009, Ye and Chang published an improved reaction with two other catalysts, *i.e.*, MoO₂(acac)₂ and Ph₃PO.^[9]

More recently, catalyst-based reactions have been examined, such as using vanadium as a catalyst^[10] in an IPy₂BF₄[−] promoted Meyer-Schuster rearrangement of propargylic esters.^[11] Furthermore, iodine (I₂) and *N*-iodosuccinimide promoted rearrangements have been used to prepare α -iodo- α,β -unsaturated esters from 3-alkoxy-2-yn-1-ols^[10] and α -iodo- α,β -unsaturated ketones from propargyl alcohols.^[13]

Reaction Mechanism

In the early studies, no reaction mechanism was proposed for the Meyer-Schuster rearrangement leading to α -iodo compounds. In 2007, Chen and Wang^[7] proposed the mechanism, which starts from the acid catalyzed β -elimination and attack by iodide into the positively charged β -carbon leading to the formation of cumulated diene intermediate **1a** (Figure 2A). The intermediate **1a** is proposed to lead to the loss of the iodine radical through bond cleavage to form an iodo peroxide intermediate **1b** that breaks down into radical **1c**. Finally, the radical scavenges the iodine radical to form α -iodo aldehyde **2**. The radical mechanism was supported by the disturbance of the reaction by the presence of a radical scavenger TEMPO.^[7]

Ye and Zhang^[9] proposed a mechanism based on the formation of cumulated diene **4** through an intermediate **3a** (Figure 2B) by the 3,3-rearrangement.^[9] Other interactions between hydroxyl group and catalyst, a metal ion, or a promoter molecule have also been proposed, *e.g.*, oxygen of tosyl-ester,^[11] oxovanadate,^[14] or HOI.^[13] Recently, Baire and Sadhukhan postulated a novel mechanism with a cyclic intermediate **4** (Figure 2C).^[15]

Figure 2 Reaction mechanisms proposed in the literature. A Radical mechanism. B Oxovanadate catalyzed mechanism. C. Cyclic intermediate mechanism.

Stereochemistry of α,β -Double Bond

Both Chen and Wang^[5] and Yu *et al.*^[6] described a mixture of *E* and *Z*-isomers with asymmetric tertiary alcohols. However, the *Z*-isomers were predominant in the case of secondary alcohols. Two plausible mechanisms to explain the formation of both isomers have been proposed.^[6] The differentiation was assumed to occur because of the attachment either of the gold catalyst or the iodine into the diene. *Z*-isomer was also shown to be the predominant geometry in the case of alkyl substituted alcohols.^[5,10] The stereoselective synthesis of the *E*-isomer using a vanadium catalyst was published recently.^[8]

Conclusions

The Meyer-Schuster reaction has been utilized for the preparation of α,β -unsaturated α -iodinated aldehydes, ketones and esters. Methods have evolved from the early pyridinium dichromate oxidation based reaction to sophisticated catalytic methods capable to produce a selective stereoisomer. Even although there are several metal-catalyzed and non-metal catalyzed Meyer-Schuster rearrangements described in the literature, more research is needed. With respect to future perspectives, new methods are needed to prepare complex organic molecules from simple raw materials produced from renewable sources adhering to the principles of the circular economy and sustainability. There is an urgent demand for rearrangement reactions that obey the atom economy by utilizing rearrangements of atoms and groups instead of substitution reactions.

Our group is currently developing new catalytic materials and one approach in which we are interested is the use of the Meyer-Schuster rearrangement. These results will be published soon.

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Conflict of Interest

The authors declare no conflict of interest.

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References

- [1] Zhang, D.; Fan, Y.; Yan, Z.; Nie, Y.; Xiong, X.; Gao, L. Reactions of α -haloacroleins with azides: highly regioselective synthesis of formyl triazoles. *Green Chem.* **2019**, *21*, 4211–4216.
- [2] Williams, R. D.; Bawel, S. A. General Methodology for the Preparation of Unsymmetrical α -Linked Bisenones via Ligandless Cross-Coupling Reactions. *Org. Lett.* **2017**, *19*, 1730–1733.
- [3] Meyer, K. H.; Schuster, K. Umlagerung tertiärer Äthynyl-carbinole in ungesättigte Ketone. *Ber. Dtsch. Chem. Ges. (A and B Series)* **1922**, *55*, 819–823.
- [4] Justaud, F.; Hachem, A.; Grée, R. Recent developments in the Meyer-Schuster rearrangement. *Eur. J. Org. Chem.* **2021**, *4*, 514–542.
- [5] Roy, D.; Tharra, P.; Baire, B. Intercepted Meyer-Schuster Rearrangements in Organic Synthesis. *Asian J. Org. Chem.* **2018**, *6*, 1015–1032.
- [6] Antonioletti, R.; D'Auria, M. M.; Piancatelli, G.; Scettri, A. Pyridinium dichromate in organic synthesis: a convenient oxidation of α -ynol-iodine complexes to α,β -unsaturated α -iodo-aldehydes. *Tetrahedron Lett.* **1981**, *22*, 1041–1042.
- [7] Chen, S.; Wang, J. One-pot synthesis of α -iodo-substituted α,β -unsaturated aldehydes from propargylic alcohols. *J. Org. Chem.* **2007**, *72*, 4993–4996.
- [8] Yu, M.; Zhang, G.; Zhang, L. Gold-catalyzed efficient preparation of linear α -iodoenones from propargylic acetates. *Org. Lett.* **2007**, *9*, 2147–2150.
- [9] Ye, L.; Zhang, L. Practical synthesis of linear α -iodo/bromo- α,β -unsaturated aldehydes/ketones from propargylic alcohols via Au/Mo bimetallic catalysis. *Org. Lett.* **2009**, *11*, 3646–3649.
- [10] Trost, B. M.; Tracy, J. S. Vanadium-Catalyzed Synthesis of Geometrically Defined Acyclic Tri- and Tetrasubstituted Olefins from Propargyl Alcohols. *ACS Catal.* **2019**, *9*, 1584–1594.
- [11] Suárez-Rodríguez, T.; Suárez-Sobrinho, A. L.; Ballesteros, A. Direct Synthesis of α -Iodoenones by IPy2BF₄-Promoted Rearrangement of Propargylic Esters. *J. Org. Chem.* **2018**, *83*, 12575–12583.
- [12] Puri, S.; Thirupathi, N.; Sridhar, R. M. Iodo Meyer-Schuster Rearrangement of 3-Alkoxy-2-yn-1-ols for β -Mono (Exclusively *Z*-Selective)-Disubstituted α -Iodo- α,β -Unsaturated Esters. *Org. Lett.* **2014**, *16*, 5246–5249.
- [13] Zhu, H. T.; Fan, M. J.; Yang, D. S.; Wang, X. L.; Ke, S.; Zhang, C. Y.; Guan, Z. H. An iodine-promoted Meyer-Schuster rearrangement for the synthesis of α -iodo unsaturated ketones. *Org. Chem. Front.* **2015**, *2*, 506–509.
- [14] Antiñolo, A.; Carrillo-Hermosilla, F.; Cadierno, V.; Álvarez, J. G.; Otero, A. Microwave-assisted Meyer-Schuster rearrangement of propargylic alcohols catalyzed by the oxovanadate complex [V(O)Cl(OEt)₂]. *ChemCatChem* **2012**, *4*, 123–128.
- [15] Baire, B.; Sadhukhan, S. Formal halo-Meyer-Schuster rearrangement of propargylic acetates through a novel intermediate and an unexampled mechanistic pathway. *Chem.-Eur. J.* **2019**, *42*, 9816–9820.

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