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Valorization of methyl azelaaldehydate – a vegetable oil-based platform molecule – to monomers through Stetter reaction

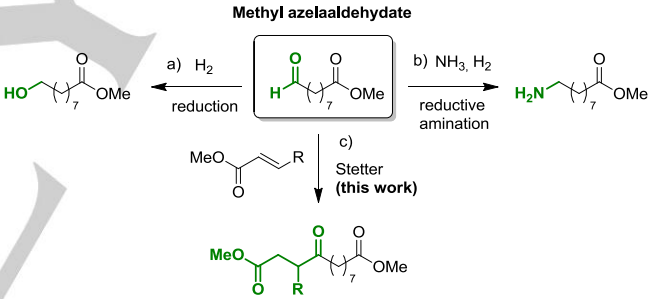
Aubin Charvieux,[a] Nam Duc Vu,[a] Nicolas Duguet*[a] and Marc Lemaire*[a]

Abstract: The valorization of vegetable oil-derived methyl azelaaldehydate (methyl 9-oxo-nonanoate) to monomers was studied through NHC-catalysed Stetter reaction. Among the Michael acceptors tested, dimethyl fumarate gave the highest selectivity (97 %) for the corresponding Stetter adduct, thus limiting the competing benzoin condensation.

Introduction

Biomass has received considerable attention in the recent years as a sustainable alternative to petroleum derivatives.[1] In this regard, vegetable oils represent a valuable feedstock as they are widely available and relatively inexpensive. Contrary to lignin or carbohydrates, they have low oxygen content, thus making them perfectly suitable for biofuel applications.[2] However, these valuable resources can be best transformed to bio-based platform chemicals[3] and polymers[4] with higher added values. This strategy is also beneficial from an environmental point of view, as it incorporates CO_2 in materials instead of releasing it in the atmosphere.

Three main approaches are reported in the literature to convert vegetable oils to polymers: i) unsaturated vegetable oils and their corresponding epoxidized derivatives can be directly (co-)polymerized to give functional materials such as linoleum, alkyd resins or epoxy resins; ii) unsaturated fatty acids can be also functionalized to produce monomers through a wide range of transformations; iii) unsaturated fatty acids can be cleaved to give shorter fragments that can be further transformed to polymer building-blocks. This last strategy is particularly attractive as short monomers (C6-C12) usually give access to materials with better mechanical properties. For example, methyl ricinoleate obtained from castor oil can be thermally cracked to give heptanal and methyl 10-undecenoate that is further transformed to nylon-11 (Rilsan®).[5] Terminal alkenes can also be produced by cross-metathesis of unsaturated fatty acid derivatives with ethylene (ethenolysis).[6] The alkenes can be further transformed to the corresponding homologated aldehydes through hydroformylation.[7] Advantageously, functionalized aldehydes can be directly obtained by reductive ozonolysis of unsaturated fatty acid derivatives.[8] Specifically, the reductive ozonolysis of methyl oleate gives nonanal and methyl azelaaldehydate (methyl 9-oxo-nonanoate) as cleavage compounds and each of them could be valorized following their own value chain. Nonanal can be used as such or serves as an alkylating agent for the preparation of 100% biobased surfactants through aldolisation[9] or reductive alkylation (reductive etherification) of polyols[10] and sugar derivatives.[11] Comparatively, there are not so many ways to valorize methyl azelaaldehydate. On the one hand, the reduction of its aldehyde function gives the corresponding alcohol and the resulting monomer - methyl 9-hydroxynonanoate - can be further (co-)polymerized to give polyesters (Scheme 1, a).[12] On the other hand, the reductive amination with ammonia affords methyl 9-aminononanoate that serves as a monomer for the preparation of polyamide-9 or mixed polyamides (Scheme 1, b).[13] In this context, complementary routes to valorize methyl azelaaldehydate are of great interest.



Scheme 1. Valorization of methyl azelaaldehydate to monomers.

Recently, organocatalysis has emerged as a new tool for the valorization of biomass.[14] Among available organocatalysts, *N*-Heterocyclic carbenes (NHCs)[15] occupy a unique place as they can promote *Umpolung* reactivity.[16] This specific reactivity has been notably exploited for the valorization of bio-based aldehydes such as furfural, 5-hydroxymethylfurfural (HMF)[17] and bioethanol-derived acetaldehyde through Benzoin condensation.[18] The Stetter reaction,[19] *i.e.* the 1,4-addition of an aldehyde onto a Michael acceptor, also employs *Umpolung* reactivity and has been extensively studied in both intra-[20] and intermolecular versions.[21] However, it has been by far less studied in the context of the valorization of biomass. To the best of our knowledge, only Chi *et al.* have reported the use of the Stetter reaction to trap formaldehyde equivalents – generated from hexoses through retro-benzoin condensation – with enones to give the corresponding β-formylketones.[22]

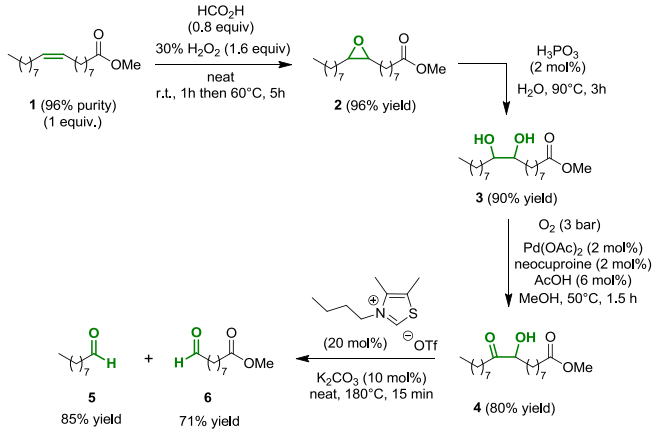
In this context, we report herein a complementary route for the valorization of methyl azelaaldehydate by NHC-catalyzed Stetter reaction with acrylates to give functionalized monomers (Scheme 1, c).

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Results and Discussion

Methyl azelaaldehydate can be prepared from methyl oleate through reductive ozonolysis. However, this method requires specific equipment and is dangerous due to the toxicity of ozone and the formation of explosive intermediates. That is the reason why, it was synthesized following our previously reported procedure (Scheme 2).

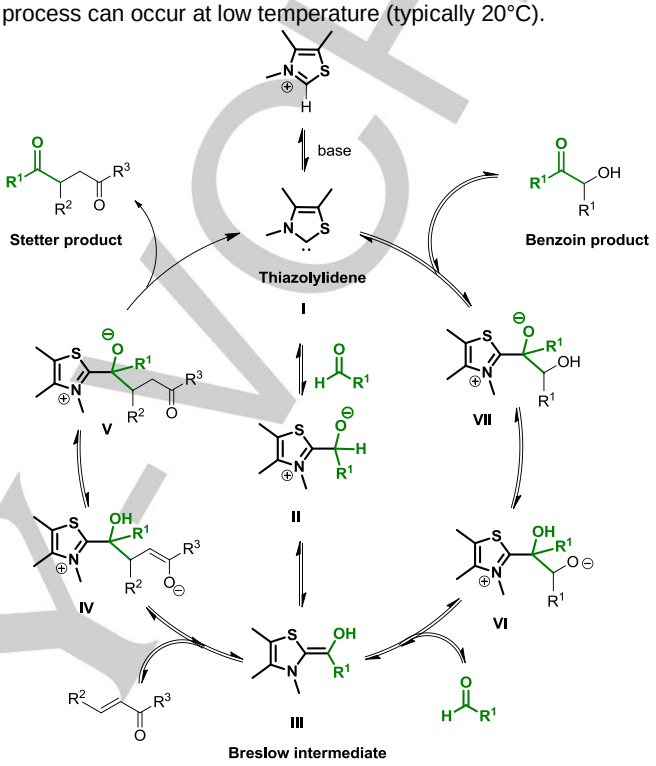


Scheme 2. Preparation of methyl azelaaldehydate from methyl oleate.

First, methyl oleate **1** (96% purity) was epoxidized to methyl 9,10-epoxystearate **2** in 96% isolated yield.[23] The epoxide was then hydrolyzed, giving methyl 9,10-dihydroxystearate **3** in 90% isolated yield. This diol was selectively oxidized using a $Pd(OAc)_2$ / neocuproine complex under oxygen atmosphere to give α-hydroxyketone **4** with 80% yield.[24] Alternatively, it can also be prepared by dehydrogenation of diol **3** using Ru/C with removal of hydrogen under vacuum.[24] Finally, the cleavage of **4** through NHC-catalysed retro-benzoin process gave aldehydes **5** and **6** under reactive distillation conditions, with 85 and 71% yields, respectively.[25]

With methyl azelaaldehydate **6** (GC purity = 98%) in hands, we envisioned that the Stetter reaction using a range of acrylates as Michael acceptors would provide multi-functional compounds that could serve as monomers for polymer applications. To find appropriate reaction conditions, methyl acrylate was selected as a model substrate. The Stetter reaction between methyl azelaaldehydate **6** and methyl acrylate was already reported by Novák *et al.*[26] The Stetter adduct was obtained in only 42% yield. However, the corresponding symmetrical α-hydroxyketone was also formed in 58% yield, showing that the benzoin condensation is a competing reaction. This reaction has not been further optimized by the authors as the desired product was only an intermediate in the preparation of prostaglandin synthons.

From a mechanistic point of view, the Stetter reaction and the benzoin condensation both occur through the common Breslow intermediate[27] **III** formed by the nucleophilic addition of carbene **I** onto the aldehyde (Scheme 3). Thus, the selectivity between Stetter and benzoin products is directly correlated to the reaction between the Breslow intermediate and the present electrophiles (aldehyde or Michael acceptor). In most cases, the aldehyde is by far more reactive than the Michael acceptor, leading to the α-hydroxyketone as primary product. However, considering that the benzoin condensation is a reversible process while the Stetter reaction is not, the Stetter adducts can be produced as final products, as these species are usually thermodynamically favored.[28] With aromatic aldehydes (R^1 = Ar), the reverse process can occur at low temperature (typically 20°C).



Scheme 3. Stetter and benzoin condensation competing reaction mechanisms.

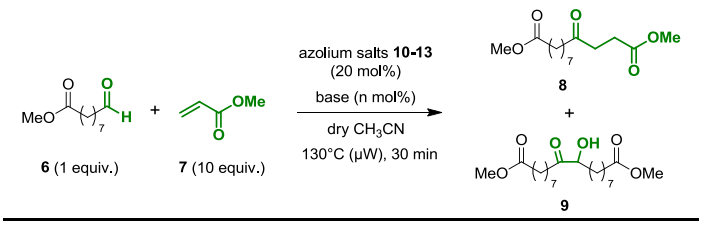
Consequently, aromatic α-hydroxyketones, *i.e. benzoins*, can be used as aldehyde precursors for the Stetter reaction.[29] In contrast, the α-hydroxyketones produced from aliphatic aldehydes (R^1 = alkyl), *i.e. acyloins*, are by far more stable than their aromatic analogues. Therefore, the retro-*acyloin* process can only occur at elevated temperature (typically 130°C) and can only be catalyzed by thiazolylidene species generated from the corresponding thiazolium salts, as reported by Miyashita,[30] Chi[22] and our group,[25] and supported by DFT calculations.[31]

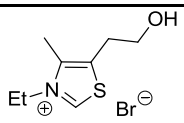
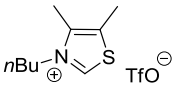
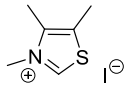
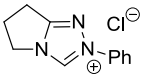
From these previous results and mechanistic considerations, we have first investigated the Stetter reaction of methyl azelaaldehydate **6** with methyl acrylate using a small range of thiazolium precatalysts at 130°C under microwave irradiation (Table 1).[32]

With commercially available thiamine-derived thiazolium salt **10** (20 mol%) and K_2CO_3 (10 mol%), the conversion of **6** reached 59% and Stetter adduct **8** was obtained with only 27% yield (Table 1, entry 1). Under these conditions, α-hydroxyketone **9** was also formed with 18% yield. With our home-made[25b] thiazolium triflate **11**, the conversion improved to 89% and **8** was obtained with 48% yield (Table 1, entry 2). Slightly better results were obtained with commercially-available thiazolium **12**, giving **8** with 50% yield (Table 1, entry 3). Finally, triazolium salt **13**,

used as negative control, gave no Stetter product and only yielded the self-aldolisation of aldehyde **6**, confirming again the superiority of thiazolylidene species to catalyze the desired transformation (Table 1, entry 4). From these results, thiazolium salt **12** was chosen as a precatalyst for further optimization.

Table 1. Azolium precatalyst screening.[a]

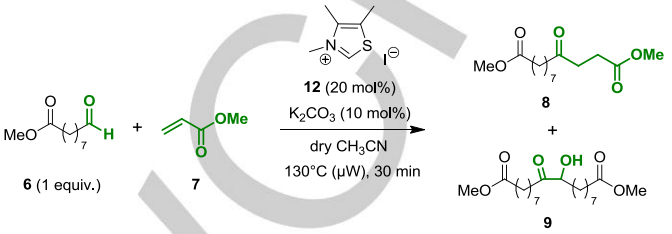


Entry	Azolium salt		Conv.[b][%]	Yield[b] [%]	
			6	**8**	**9**
1		**10**	59	27	18
2		**11**	89	48	28
3		**12**	92	50	33
4		**13**	56	0	0

[a] Conditions: microwave tube, aldehyde **6** (1 equiv., 1 mmol), **7** (10 equiv.), azolium salt (20 mol%), K_2CO_3 (10 mol%) for precatalyst **10-12** or *t*BuOK (20 mol%) for precatalyst **13**, dry CH_3CN (1.5 mL), 130°C (μW), 30 min; [b] the conversions and yields were determined by GC using hexadecane as internal standard.

The effect of the quantity of Michael acceptor **7** has then been next studied (Table 2). As expected, the yield in Stetter product **8** progressively increased between 2.6 and 10 equivalents of methyl acrylate (Table 2, entries 1-3). Further increase to 15 equivalents did not lead to significant improvement, as the selectivity only increased slightly (Table 2, entry 4). Consequently, 10 equivalents of methyl acrylate were selected as a good compromise. Finally, increasing the reaction time under our best conditions (Table 2, entry 3) did not improve significantly the results. Overall, under the best conditions, the desired Stetter product **8** was afforded with only 50% yield, while the undesired acyloin **9** was obtained in 33% yield. This moderate selectivity could be explained by the low electrophilicity of methyl acrylate. This assumption is supported by Domingo *et al.* in a DFT study aiming at classifying several Michael acceptors according to their reactivity toward nucleophilic addition.[33] Keeping in mind that the objective is to synthesize aliphatic Stetter products with suitable functional groups for polymerization, a range of Michael acceptors was tested under the best conditions (Table 3). Fumaric acid **14** did neither give the Stetter product nor the acyloin (Table 3, entry 1). This can be explained by its insolubility in acetonitrile and the fact that it can react with the base, thus preventing the formation of the active carbene species.

Table 2. Effect of the quantity of Michael acceptor.



Entry	Quantity of **7** [equiv.]	Conv.[b][%] **6**	Yield[b] [%]	
			8	**9**
1	2.6	93	23	52
2	5	91	37	43
3	10	92	50	33
4	15	83	52	26

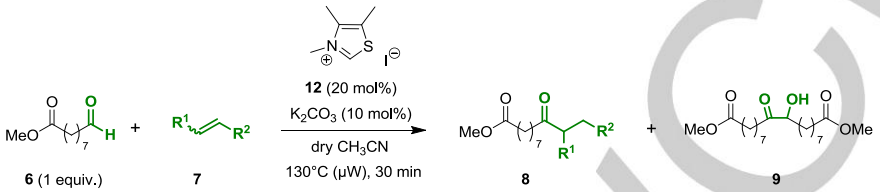
[a] Conditions: microwave tube, aldehyde **6** (1 equiv., 1 mmol), **7**, thiazolium salt **12** (20 mol%), K_2CO_3 (10 mol%), dry CH_3CN (1.5 mL), 130°C (μW), 30 min; [b] the conversions and yields were determined by GC chromatography using hexadecane as internal standard.

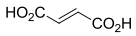
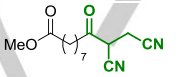
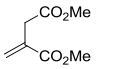
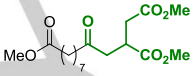
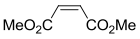
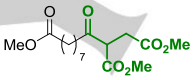
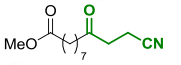
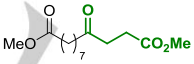
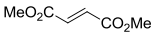
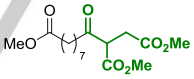
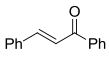
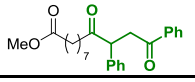
Surprisingly, no reaction occurred with maleic anhydride **15**, though this compound is one of the most electrophilic Michael acceptors (Table 3, entry 2).[33,34] Consequently, we hypothesized that the carbene formed from thiazolium **12** could directly add onto maleic anhydride instead of the aldehyde, thus giving a stable species and trapping the catalyst. Fumaronitrile **16** gave a high selectivity for the Stetter adduct **22** (94%) but this result is not very representative considering that the conversion was very low (Table 3, entry 3). With dimethyl itaconate **17**, the conversion improved to 27% but almost no selectivity was observed (Table 3, entry 4). The use of dimethyl maleate **18** and acrylonitrile **19** gave good conversions (88%) but moderate selectivity for the Stetter products **24** and **25** (50 and 72% respectively) (Table 3, entries 5-6). Slightly better results were obtained with methyl acrylate under these reaction conditions (Table 3, entry 7). Dimethyl fumarate **20** gave a good 85:15 selectivity for the triester **24** but the conversion remained modest (65%) (Table 3, entry 8). Satisfyingly, when using 5 equivalents of **20**, the selectivity towards the Stetter adduct **24** improved to 97% after 1 hour (Table 3, entry 9). Moreover, when using chalcone **21** as a starting material, the corresponding Stetter adduct **26** was obtained with 93% selectivity at complete conversion (Table 3, entry 10). These results show that the selectivity could be switched in favor of the Stetter adduct, even with aliphatic aldehydes, provided a suitable Michael acceptor. In our case, the most suitable Michael acceptors should have an

intermediate electrophilicity, *i.e.*, an electrophilicity parameter *E* between -17 and -19, according to Mayr.[34]

Interestingly, when using dimethyl fumarate, the reaction also gave diester **8** as a byproduct (see GC chromatogram in ESI). We thus hypothesized that Stetter adduct **24** could undergo decarboalkoxylation in the presence of traces of water, thus giving product **8** (Scheme 4). A similar reaction was previously reported by Curran *et al.*, showing that microwaves play an important role in this process.[35] In order to confirm this hypothesis, a solution of crude triester **24** was treated with water and K_2CO_3 and the reaction mixture was heated at 180°C under microwave irradiation for 1.5 hour.

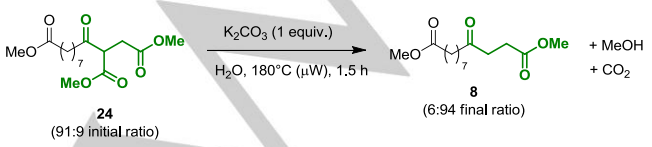
Table 3. Stetter adduct/acyloin selectivity for a range of suitable Michael acceptors.[a]



Entry	Michael acceptor		Conv.[b][%] 6	Stetter adduct		GC ratio[b] [%] Stetter adduct	GC ratio[b] [%] Acyloin 9
1		**14**	-	-	-	-	-
2		**15**	-	-	-	-	-
3		**16**	7		**22**	94	6
4[c]		**17**	27		**23**	54	46
5[c]		**18**	88		**24**	50	50
6[c]		**19**	88		**25**	72	28
7[c]		**7**	92		**8**	79 (27)[e]	21
8[c]		**20**	65		**24**	85	15
9[d]			95			97 (48)[e]	3
10		**21**	99		**26**	93 (82)[e]	7

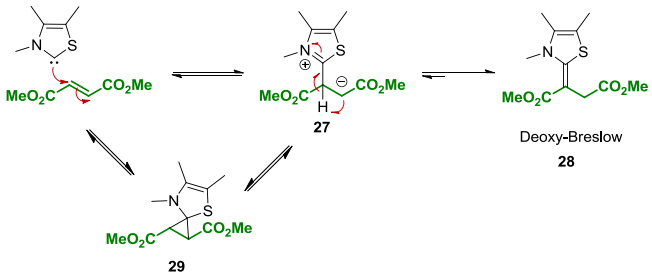
[a] Conditions: microwave tube, aldehyde **6** (1 equiv., 1 mmol), Michael acceptor (5 equiv), thiazolium salt **12** (20 mol%), K_2CO_3 (10 mol%), dry CH_3CN (1.5-2 mL), 130°C (μW), 30 min; [b] the conversions and ratios were determined by GC chromatography. [c] 10 equiv of Michael acceptor. [d] Reaction time = 1h. [e] The isolated yields obtained after column chromatography are given in brakets.

Under these conditions, the initial 91:9 ratio between products **24** and **8** switched to 4:96 in favor of **8**, thus confirming our hypothesis. Finally, considering that it is difficult to produce **8** with high selectivity from the direct Stetter reaction with methyl acylate, the decarboalkoxylation of **24** offers an interesting alternative to access this diester.



Scheme 4. Decarboalkoxylation of **24** to diester **8**.

Furthermore, within the frame of this study, we have also identified diester **28**, incorporating a thiazole ring and a dimethyl fumarate moiety (Scheme 5). The structure has been assigned by ^1H and ^{13}C NMR and confirmed by the measure of the exact mass ($[M+H]^+$ = 272.0941, see ESI for details). To account for the formation of this species, we propose that dimethyl fumarate could undergo 1,4-addition of the thiazolylidene species to give zwitterionic intermediate **27** that could rearrange to **28** through proton transfer (Scheme 5). Alternatively, a [2+1] cycloaddition between the free carbene and dimethyl fumarate could produce spirocyclopropane **29**. This spirocyclopropane species is likely to be unstable due to the ring strain and the push-pull interaction that could lead to ring-opening to give **27**.



Scheme 5. Proposed mechanism for the formation of deoxy-Breslow intermediate.

To test this hypothesis, the reaction was conducted under similar conditions but without aldehyde **6**. Under these conditions, diester **28** was observed in the crude ^{1}H NMR spectrum, thus confirming our proposal. Interestingly, diester **28** could be attributed to a deoxy-Breslow intermediate. Deoxy-Breslow intermediates of triazolylidene and imidazolylidene species have been already reported when using alkyl halides,[36] acrylates[37] or chalcones.[38] However, to the best of our knowledge, deoxy-Beslow species have never been observed with thiazolylidene species. Consequently, the catalytic activity of **28** has been probed on the Stetter reaction under the same conditions reported in Table 3, entry 8 (with or without K_2CO_3). However, no Stetter adduct nor benzoin product was obtained under these conditions, indicating that **28** is relatively stable under our reaction conditions (130°C) and only zwitterionic intermediate **27** could reverse to release the free carbene.

Conclusions

In conclusion, we have developed a new valorization route of vegetable oil-derived methyl azelaaldehydate (methyl 9-oxo-nonanoate) through NHC-catalysed Stetter reaction. It was found that dimethyl fumarate gave the best results with an excellent conversion (95%) and a high selectivity (97%) for the Stetter product, thus limiting the competing benzoin condensation. The di- and triesters obtained through this methodology could serve as building-blocks for the preparation of bio-based polymers.

Experimental Section

General procedure for Stetter reaction under microwave activation: In a 5 mL microwave tube, methyl azelaaldehydate (**6**; 200 mg, 1.07 mmol, 1 equiv.), NHC precursor (**10-13**; 0.215 mmol, 0.20 equiv.), K_2CO_3 (15 mg, 0.11 mmol, 0.10 equiv), Michael acceptor in desired quantity (**7,14-21**) were combined. Dry CH_3CN (1.5 or 2 mL) was added. The mixture was stirred under microwave irradiation at desired temperature, for a period of time. The mixture was cooled to room temperature and analysed by GC (with or without hexadecane as an internal standard).

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Keywords: Aldehydes • Monomers • Stetter reaction • Umpolung • Vegetable oils

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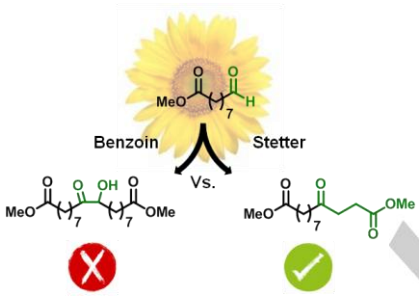
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