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Generation and cascade reactions of *N*-[1,2-bis(methoxycarbonyl)vinyl]pyridinium species

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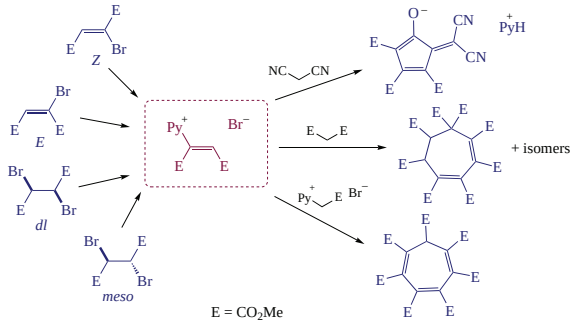
The configuration of *N*-[1,2-bis(methoxycarbonyl)vinyl]-pyridinium intermediate generated from stereoisomers of dimethyl dibromosuccinate or dimethyl bromobutenedioate does not depend on the precursors' configuration, as distinct from the yields and the reaction rates. The use of various nucleophiles in these cascade reactions gives either cycloheptadieneoctacarboxylic or cycloheptatrienehepta-carboxylic esters along with pyridinium 5-dicyano-methylidene-2,3,4-tris(methoxycarbonyl)cyclopenta-1,3-dien-1-olate. In the latter case, the acyclic 'Diels' golden adduct' was detected, and its structure was refined.



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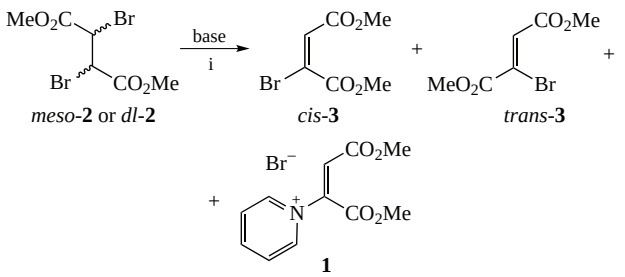
Cascade reactions are of special interest in organic synthesis due to the significant increase in molecular complexity in one stage.[1–7] Among the large number of cascade reactions involving a Michael-type addition of dimethyl acetylenedicarboxylate (DMAD), the reactions involving pyridine and its analogues are most diverse and widely studied.[8–15] However, the use of DMAD has several significant disadvantages such as its relatively high price, a tendency to polymerize upon storage, and pronounced lachrymatory properties. Since DMAD is highly reactive to pyridine itself to form bicyclic products,[16,17] the cascade reactions usually require the use of pyridine with acetic acid to suppress the formation of the bicyclic products. We have recently shown that the key intermediate in these reactions is *N*-[1,2-bis(methoxycarbonyl)vinyl]pyridinium **1**[18] (Scheme 1) which can be generated from more convenient dimethyl dibromo-succinate **2** or bromomaleate *cis*-**3**.[18,19] It is noteworthy that DMAD can be obtained from dibromosuccinic acid; however, this procedure is more complicated.

It is worth noting that in some works dealing with dibromosuccinates, the stereochemistry is either not mentioned or not taken into account.[19–21] In one case[22] this neglecting could be the reason for the low yield of the target dihydrofuran derivative which was attempted to be accessed from a *trans*-butenediol derivative (instead of *cis*-) obtained, in turn, from *dl*-dibromosuccinate. The aim of our work was to investigate the influence of the stereochemistry of the alternative sources of **1** onto reaction times and product yields in key cascade reactions involving **1**.



Scheme 1 *Reagents and conditions*: i, Et_3N or pyridine, DMF, room temperature, 2.5 h.

It is known[23,24] that dehydrobromination of dibromosuccinates occurs through E2 mechanism and follows *anti* elimination. Most authors state that a single isomer is formed in each case. We have examined the stereoselectivity of elimination in both *meso*- and *dl*-succinic acid methyl esters with either triethylamine or pyridine at full conversions. Both bases gave mostly *anti* elimination products (see Scheme 1 and Table 1). In the case of pyridine, side formation of salt **1** was observed whose content increased with the use of two equivalents of the base. Elimination in *dl*-**2** proceeds more selectively than in *meso*-**2** in DMF since the most stable conformation in *dl*-**2** corresponds to *anti* elimination. Preparative large-scale experiments in ether

Table 1 Elimination of HBr from *meso*-**2** or *dl*-**2**.[a]

Entry	Substrate	Base (equiv.)	Ratio *cis*-**3**/*trans*-**3**/**1**
1	*meso*-**2**	Et_3N (1)	87 : 13 : 0
2	*meso*-**2**	Pyridine (1)	84 : 8 : 8
3	*meso*-**2**	Pyridine (2)	65 : 6 : 29
4	*dl*-**2**	Et_3N (1)	3 : 97 : 0
5	*dl*-**2**	Pyridine (1)	2 : 98 : 0
6	*dl*-**2**	Pyridine (2)	2 : 92 : 6

[a] DMF, room temperature, 2.5 h (see Scheme 1).

provided lower selectivity, so individual *cis*-**3** and *trans*-**3** were obtained upon rectification and directional crystallization, respectively.

Further we have studied the reaction of either *cis*-**3** or *trans*-**3** with pyridine in DMF under conditions similar to those in the cascade reactions.[18,19] Curves *1* and *3* in Figure 1 were obtained from experiments with the addition of trifluoroacetic acid. NMR monitoring revealed that both isomers were converted into the same ion **1** whose configuration was proposed as *E* since it must be most stable. The formation of **1** from *cis*-**3** (see Figure 1, curve *2*) proceeds much more rapidly than from *trans*-**3**, and the kinetic curve *4* for pyridinium salt formed from *trans*-**3** grew exponentially, which was not typical for any reaction order. We assumed that this type of curve can be explained by the autocatalytic nature of the reaction. Since the cascade reactions involving **1** are accompanied by the formation of oligomeric products with the elimination of pyridinium hydrobromide, we assume that general acid catalysis takes place here. Therefore, we obtained the *N*-vinylpyridinium salt **1** from both isomers in the presence of the initial amount of pyridinium ion (by adding 1 equiv. of trifluoroacetic acid to the reaction mixture). Both reactions were significantly accelerated in more acidic media (curves *1*, *3*). Since compound **1** and starting *cis*-**3** and *trans*-**3** are further consumed in side processes this only gives a qualitative estimation of the reaction rates while the determination of the reaction rate constants is challenging.

The influence of the source of *N*-[1,2-bis(methoxycarbonyl)-vinyl]pyridinium **1** onto reaction yields was studied in the three most important cascade reactions that give valuable compounds (Scheme 2).[18–20,25,26] The first reaction leading to isomeric octa(methoxycarbonyl)cycloheptadienes **4** was first reported by Diels[16] wherein **1** was generated from DMAD. Recently, we showed that compound **4** could be obtained from *cis*-**3** and we first provided evidence that **1** was the key intermediate in that reaction. The second reaction was the synthesis of pyridinium 5-dicyanomethylidene-2,3,4-tris(methoxycarbonyl)cyclopenta-1,3-dien-1-olate **5** which was also first obtained by Diels from DMAD.[16] In 2021, we replaced DMAD with dimethyl dibromo-succinate in this synthesis,[20] but we did not pay attention to its configuration. A unique cascade reaction involving **1** is the formation of heptamethyl cyclohepta-1,3,5-triene-1,2,3,4,5,6,7-heptacarboxylate **6**. Unlike in the two previous reactions it is impossible to generate **1** from DMAD, since the starting pyridinium salt reacts with it. In each reaction, the key intermediate **1** was generated from four different precursors and the yields and reaction times are given in Table 2.

In the case of reactions *A* and *C* (see Scheme 2), reactants *cis*-**3** and *meso*-**2** (the latter gives *cis*-**3** upon elimination) provide higher yields than *trans*-**3** and *dl*-**2** even at longer reaction times. Unusual behavior in these terms is demonstrated by reaction *B*. If in the above cases the highest yields of the target compounds were obtained from *cis*-**3**, the reaction *B* conversely gave lowest yield from *cis*-**3** and the product was isolated in a mixture with an unknown compound (see Table 2, entry 5). Previously

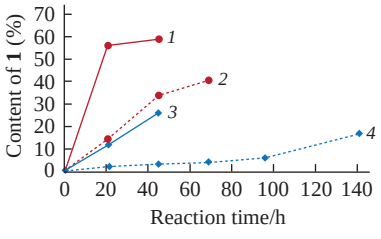
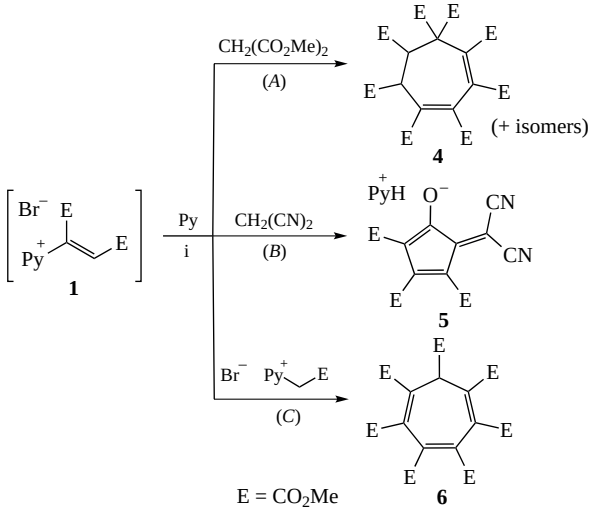


Figure 1 Kinetic curves for the formation of salt **1** from *cis*-**3** in the presence (*1*) and in the absence (*2*) of TFA and from *trans*-**3** – curves (*3*) and (*4*), respectively.



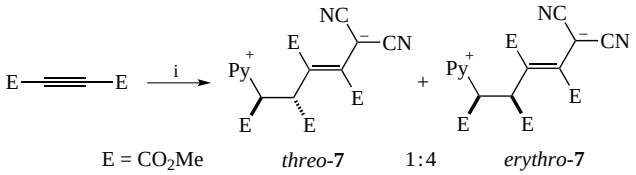
Scheme 2 *Reagents and conditions*: i, Py, DMF, room temperature; for the reaction time and source of **1**, see Table 2.

Table 2 Cascade reactions of *N*-[1,2-bis(methoxycarbonyl)vinyl]-pyridinium **1**.

Entry	Reactant	Precursor of **1**	*t*/days	Product	Yield (%)
1	$CH_2(CO_2Me)_2$	*cis*-**3**	5	**4**	63
2	$CH_2(CO_2Me)_2$	*trans*-**3**	16	**4**	32
3	$CH_2(CO_2Me)_2$	*meso*-**2**	5	**4**	58 (74[a])
4	$CH_2(CO_2Me)_2$	*dl*-**2**	16	**4**	28
5	$CH_2(CN)_2$	*cis*-**3**	21	**5**	17[b]
6	$CH_2(CN)_2$	*trans*-**3**	28	**5**	53
7	$CH_2(CN)_2$	*meso*-**2**	21	**5**	62
8	$CH_2(CN)_2$	*dl*-**2**	28	**5**	34
9	$Py^+CH_2CO_2Me$	*cis*-**3**	4	**6**	52
10	$Py^+CH_2CO_2Me$	*trans*-**3**	12	**6**	29
11	$Py^+CH_2CO_2Me$	*meso*-**2**	4	**6**	51
12	$Py^+CH_2CO_2Me$	*dl*-**2**	12	**6**	27

[a] In a 50 g scale of *meso*-**2**. [b] NMR yield from a mixture with intermediate product *threo*-**7**.

Cookson *et al.*[27] reported that in original paper Diels incorrectly established the structure of a compound, which was referred to as 'Diels' golden adduct', obtained from DMAD, pyridine and malononitrile. That compound gave **5** upon cyclization. The structure of the 'golden adduct' given by Cookson did not correspond to our spectral data in experiment 5 (see Table 2). We reproduced the Diels' synthesis and obtained a product which was not a salt proposed by Cookson but represented a mixture of isomeric zwitter-ionic compounds *threo*-**7** and *erythro*-**7** in a ratio of 1 : 4 (Scheme 3). Moreover, we found that it was *threo*-**7** which was observed in our experiment and was not transformed into **5** with increased reaction time, but was converted into **5** when heated with pyridine. The diastereomer configuration was assigned on the basis of the spin–spin coupling constants between H^4 and H^5 (8.8 Hz for *erythro*-**7** and 7.4 Hz for *threo*-**7**), which are usually larger for the isomer with the antiperiplanar protons (*cf.* ref. 28). The configuration of the double bond is proposed as *E* based on the regiochemistry of the cyclization of



Scheme 3 *Reagents and conditions*: i, AcOH, Py, $CH_2(CN)_2$, room temperature.

both isomers into **5**, wherein the attack by the C^2 carbon atom at the carbonyl group at C^5 is required.

Additionally, we analyzed experiments 5 and 6 (see Table 2) at low conversions, when product **5** was hardly observed, and found that *trans*-**3** gave *erythro*-**7** predominantly (ratio 3 : 1), while the *threo* diastereomer was predominantly formed from *cis*-**3** (ratio 3 : 1). This observation is especially interesting, since we established that pyridinium salt **1** is formed from all sources, so this stereoselectivity does not appear from the double bond configuration in the starting compounds. Thus, we assume that the *erythro* isomer is first formed in all reactions; however, in the case of *cis*-**3**, it transforms into the less reactive *threo* isomer faster than into **5**. On the other hand, *meso*-**2**, which is converted into *cis*-**3** upon elimination, provides a good yield due to the formation of one equivalent of pyridinium bromide in the beginning. Anyway, the nature of this difference in reactivity is unclear.

To conclude, we have examined isomeric esters of dibromosuccinic and bromobutenedioic acids as attractive precursors of *N*-[1,2-bis(methoxycarbonyl)vinyl]pyridinium intermediate **1** in its cascade reactions and found that the yields and reaction rates significantly depended on the precursor's configuration. The two isomers of dimethyl bromobutenedioate react with pyridine to form a single isomer of **1**, bromomaleate reacting faster than bromofumarate, however both reactions are accelerated in the presence of pyridinium cation. Since the synthesis of bromobutenedioates from succinates is an additional reaction step and the reactions are catalyzed by pyridinium bromide, the use of dibromosuccinic acid esters in the syntheses seems most attractive.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.037.

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