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Synthesis of Chiral Esters of Acetylenedicarboxylic Acid

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Abstract: A general method for the preparation of acetylenedicarboxylic acid esters has been investigated and several esters have been prepared in excellent yield. The bis-(methyl (*S*)-lactyl), bis-(methyl (*R*)-mandelyl), and bis-menthyl esters were prepared, as well as achiral diaryl and dialkyl esters. The esters were synthesized from the corresponding dibromofumarates by 2,3-dibromo elimination using zinc or zinc amalgam in THF at room temperature or at reflux. The dibromofumarates were prepared by the esterification of dibromofumaryl chloride with the corresponding alcohols.

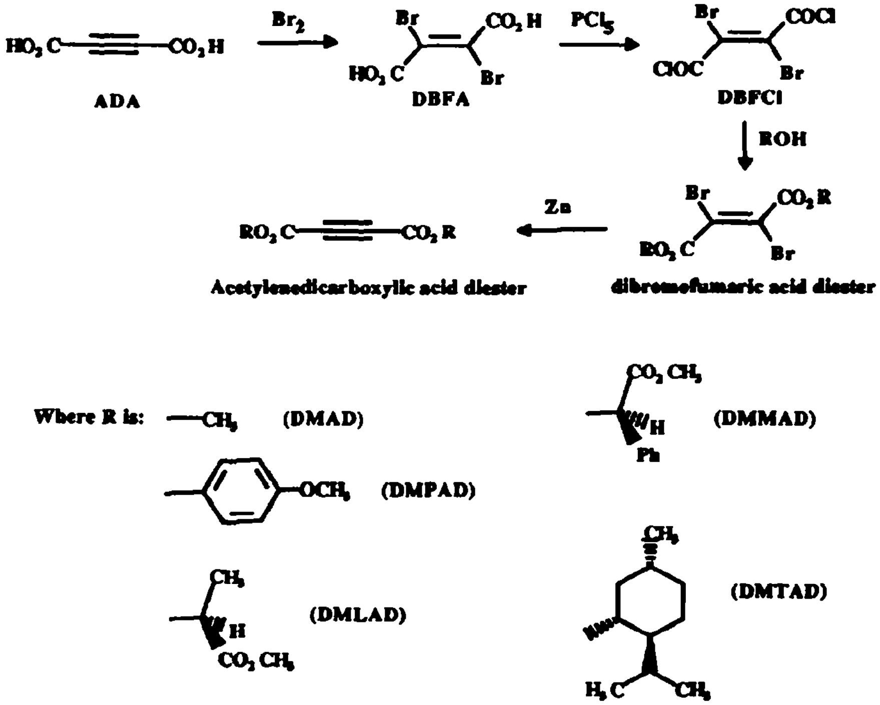
The esters of acetylenedicarboxylic acid (ADA) especially the dimethyl (DMAD) and the diethyl (DEAD) esters have been useful in organic synthesis particularly as dienophiles in cycloaddition reactions. Some of the esters themselves have also shown activity as nematocides.[1]

The synthesis of acetylenedicarboxylic acid esters can sometimes be very difficult because the triple bond polarized by the carboxylate groups is very reactive, and is often attacked surprisingly readily, even by weak nucleophiles such as phenols.[2] Although the preparation of some simple dialkyl acetylenedicarboxylates can be achieved by conventional esterification of the acid in satisfactory yield, in many instances addition to the triple bond occurs in significant amount.[3,4] It has been claimed recently that the preparation of diaryl acetylenedicarboxylates is a particularly difficult task and that direct reaction of ADA with phenols catalysed by p-toluenesulfonic acid resulted in only 14-15 % isolated yield.[5] On the other hand, Verbit *et al*[6] have claimed that they were able to prepare aryl diesters by reacting ADA with an excess of the phenol in the presence of sulfuric acid. The use of DCC as a condensing agent with DMAP as a catalyst in the esterification of ADA has been shown to be ineffective.[5]

The synthesis of acetylenedicarboxylic acid esters via the acid chloride is an impractical route because addition to the triple bond appears to be an unavoidable major reaction in many cases.[5] Besides, the preparation of the acid chloride is another difficult task to be overcome. In a recent paper it was claimed that acetylenedicarboxylic acid chloride could be prepared by treating ADA with PCl_5 but the authors were unable to isolate or purify the acid chloride due to its high reactivity.[7] Previous authors[8-10] have described their inability to prepare the acid chloride from direct chlorination of ADA with PCl_5 or $SOCl_2$ where chlorofumaryl chloride or dichloromaleic anhydride, respectively, was instead isolated. Nevertheless, Diels[10] did prepare the acid chloride in moderate yield via thermal decomposition of anthracene-9,10-endoacetylenedicarboxylyl dichloride in the presence of maleic anhydride. Attempts to prepare the acid chloride from $BrMgC{\equiv}CMgBr$ and $COCl_2$ gave only tar.[9]

Some esters of ADA can be obtained in relatively good yields via the use of the less reactive acid fluoride.[11] However, the use of highly corrosive SF_4 needed to prepare the acid fluoride constitutes an important limitation to the procedure. Moreover, addition to the triple bond was observed as an important side reaction during the preparation of a diaryl ester.

Esterification of dibromofumaryl chloride followed by dehalogenation provides an alternative route to the synthesis of acetylenedicarboxylic acid esters (Scheme 1).



Scheme 1

Dibromofumaryl chloride can be prepared by bromination of ADA followed by treatment with PCl_5. Treating the acid chloride with two equivalents of an alcohol affords the corresponding dibromofumaric acid ester, which can then be debrominated with zinc to yield the acetylenedicarboxylic acid ester. This approach was investigated in the late 1800s[12] and the early 1900s,[13] but since that time has been largely ignored except for a preparation of acetylenediamides, published in 1970.[14] We have reinvestigated the approach and found it extremely versatile. Prior bromination of ADA allows the subsequent reactions such as acid chloride formation and esterification to proceed without the formation of addition products which have been frequently observed in the direct reactions of ADA with $SOCl_2$, PCl_5, alcohols and other nucleophilic agents. Therefore, the vic-dibromide, which can then be converted to the acetylene by reductive elimination, acts as a protecting group for the reactive triple bond. This general procedure allows the preparation of many esters in excellent yield and is superior to direct esterification or transesterification methods as an excess of alcohol is not required.

We have synthesized two new chiral acetylenedicarboxylic acid esters, the bis-(methyl (*S*)-lactyl) (DMLAD) and bis-(methyl (*R*)-mandelyl) (DMMAD) esters, in order to study their asymmetric Diels-Alder reactions. The preparation of DMAD,[15] bis-4-methoxyphenyl (DMPAD),[5,6] and bis-menthyl acetylenedicarboxylates (DMTAD)[16] has been previously reported, and were prepared again by our procedure for comparison purposes. The esters were synthesized according to the general procedures shown in Scheme 1. In every case, no addition to the triple bond was observed.

Several improvements have been made to the procedures shown in Scheme 1. Bromination of ADA described by Ott[13] was laborious and time consuming. Therefore, the method used by Eichelberger[17] for the iodination of ADA was adopted with slight modification. Treatment of dipotassium ADA with bromine in NaBr solution afforded dibromofumaric acid (DBFA) in 80% yield after recrystalization from THF/hexane. Dibromofumaryl chloride (DBFCl) was made in 92% yield by stirring DBFA with PCl_5 in petroleum ether at room temperature for 5 h.[13] Thionyl chloride was unsatisfactory in this step. Without further purification, the acid chloride was added dropwise to a solution of CCl_4 containing pyridine and alcohol at 0°C to afford the diester of DBFA in > 90% yield. The conditions used for the debromination of dibromofumarates were greatly dependent on the type of the diester although the yield for these reactions was always > 85% (Table 1). Dimethyl and bis-(methyl

Table 1. Acetylenedicarboxylic Acid Esters from Debromination of Dibromofumarates.[a]

Product[b]	Reduction metal/ catalyst	Temp./time	Yield[c] (%)	mp (°C)
DMAD	granular Zn	reflux/2 h	92	-
DMPAD	granular Zn/I_2	reflux/6 h	90	145-147
DMLAD	granular Zn	reflux/4 h	95	78-81
DMMAD	Hg-Zn dust	reflux/1 h	85	-
DMTAD	Hg-Zn dust	25°C/16 h	90	131-133

[a] Dibromofumarates were used without prior purification.
[b] All new compounds were fully characterized by their spectroscopic (IR, ^1H and ^{13}C NMR, MS) and elemental analysis data.
[c] Crude Yield.

(*S*)-lactyl) esters of DBFA were debrominated with granular zinc in THF at reflux. Dimethoxyphenyl ester of DBFA required a catalytic amount of I_2 to activate the granular zinc, whereas the remaining two compounds, which have bulkier ester groups, bis-(methyl (*R*)-mandelyl) and bis-menthyl esters of DBFA, required amalgamated zinc dust. DMMAD is always contaminated with about 4 and 3 % of the corresponding fumarate and maleate, respectively, probably due to the over reduction of DMMAD.

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