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A New Synthetic Method for Allene-1,3-dicarboxylates Using DMC and a Novel Tandem Cyclization to a Pyrrolizidine Alkaloid Skeleton

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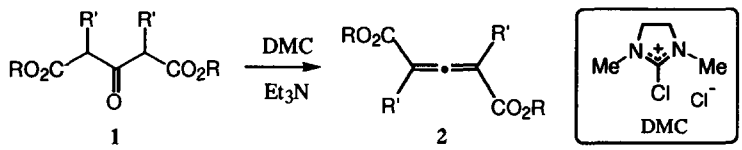
Abstract: A new one-step synthesis of allene-1,3-dicarboxylates from acetone-1,3-dicarboxylates in high yields was developed by the use of DMC as a dehydrating reagent. This process opened a new expeditious route to a 1-azabicyclo[3.3.0]octane skeleton of pyrrolizidine alkaloids from dimethyl acetone-1,3-dicarboxylate and bis(2-chloroethyl)amine *via* a Michael addition and a novel tandem cyclization.

Allenes are useful building blocks for synthetic organic chemistry.[1] Among them, we are interested in dimethyl allene-1,3-dicarboxylate (dimethyl 2,3-pentadienedioate)[2] which is a superior Michael acceptor due to its strong cationic nature on the sp carbon atom.[3] The recognized methodology for its synthesis has, however, not been satisfactory in terms of the overall yield (36%) and the multi-steps required.[2] 2-Chloro-1,3-dimethylimidazolinium chloride (DMC) is a useful reagent for esterification,[4a] amidation,[4b] selective chlorination of primary alcohol in the presence of secondary alcohol,[4c] and the synthesis of vinyl chlorides from 1,3-diketones[4d]. The last reaction prompted us to research a one-step synthesis of allene-1,3-dicarboxylates (2) from acetone-1,3-dicarboxylates (1), as shown in Scheme 1. Here we report a new synthetic method for allene-1,3-dicarboxylates (2) using DMC and its application to a facile synthesis of a pyrrolizidine alkaloid skeleton *via* a novel tandem cyclization.

Scheme 1. A Novel Synthesis of Allene-1,3-dicarboxylates



1 2

The results on the preparation of allene-1,3-dicarboxylates (2) using DMC are compiled in Table 1. The reaction of **1a** with DMC (1.2 eq.) and triethylamine (1 eq.) in dichloromethane at room temperature gave only vinyl chloride **3a** in low yield (run 1). Increasing the amount of triethylamine to two equivalents resulted in the formation of the desired dimethyl allene-1,3-dicarboxylate (**2a**) along with vinyl chloride **3a** (run 2). The treatment with three equivalents of triethylamine had the dramatic effects of enhancing of the yield of allene **2a** as well as shortening the reaction time (run 3). This reaction also worked well in α,α'-dimethyl substituted acetone-1,3-dicarboxylate **1b** to give the corresponding allene-1,3-dicarboxylate **2b** (run 4). The other esters **1c-e** also gave the desired products **2c-e** in 70-92% yields (runs 5-7).

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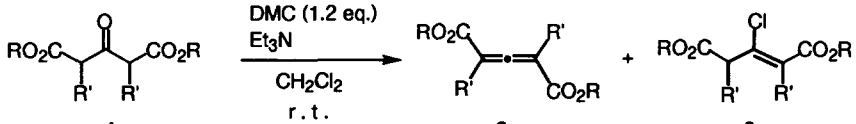
Table 1. Preparation of Allene-1,3-dicarboxylate Derivatives Using DMC [a]



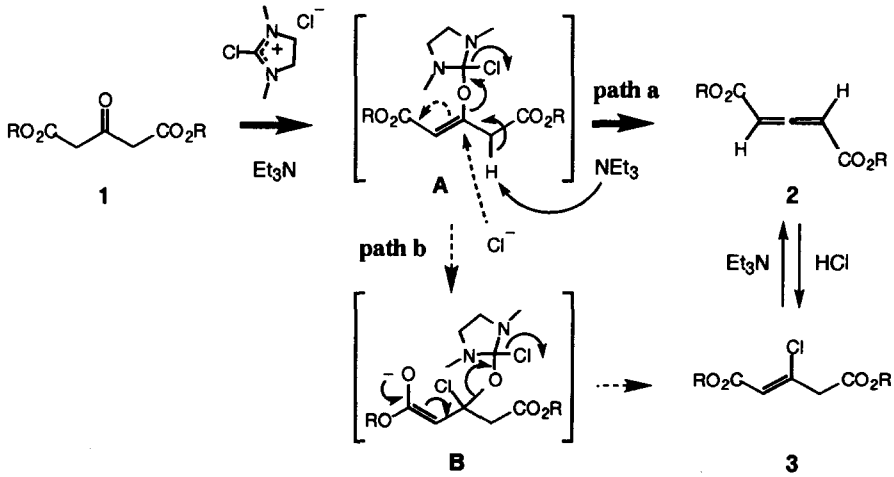
1 2 3

Entry		R	R'	Et_3N (eq.)	Time (h)	Yield (%) 2	Yield (%) 3
1	**1a**	Me	H	1	24	-	44
2	**1a**	Me	H	2	22	72	21
3	**1a**	Me	H	3	1	90	-
4	**1b**	Me	Me	3	2	73	-
5	**1c**	Et	H	3	0.5	92	-
6	**1d**	Bn	H	3	2.5	70	-
7	**1e**	^{t}Bu	H	3	0.5	71	-

a) Typical procedure (entry 3-7): To a dichloromethane (5 ml) solution of an acetone-1,3-dicarboxylate (1) (0.5 mmol) and DMC (1.2 eq.) was added triethylamine (3 eq.) at 0 °C under nitrogen atmosphere, the reaction mixture was stirred for the times indicated in the table at room temperature. The resultant mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel.

Two possible routes have been considered for the formation of allene-1,3-dicarboxylates **2**, as shown in Scheme 2. The enol derivative **A** of the ketone moiety would be initially formed by the combination of DMC and triethylamine. In the path a, triethylamine deprotonates the acidic hydrogen to produce allenes **2** directly. In the other path b, vinyl chlorides **3** could be formed by the Michael addition of a chloride anion and the subsequent elimination of 1,3-dimethyl-2-imidazolidinone; then the elimination of hydrogen chloride with triethylamine from **3** could give allenes **2**.

Scheme 2. A Plausible Reaction Mechanism

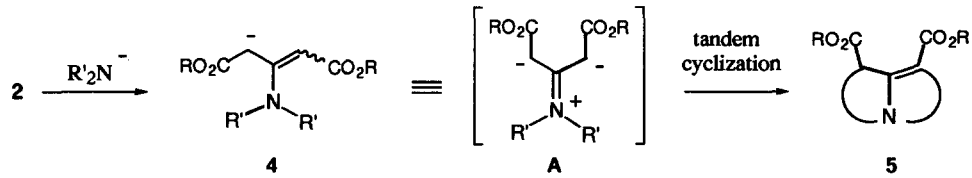


We believe that the path a is plausible because allene **2a** was initially observed on the TLC analysis, even at the initial stage of the reaction in entry 1 in Table 1; **2a** disappeared subsequently, then vinyl chloride **3a** was formed. This observation suggested that allene **2a** gave rise to vinyl chloride **3a** by the Michael addition of the

chloride anion. In addition, the formation of a half-amount of vinyl chloride **3** in the case of triethylamine (1 eq.) (entry 1) shows two equivalents of triethylamine are required in this reaction. Therefore, the possibility of path b, in which vinyl chloride **3** is formed by the use of one equivalent of triethylamine, can be ruled out. On the other hand, the partial formation of vinyl chloride in the case of triethylamine (2 eq.) (entry 2) would be attributable to partial dissociation of hydrogen chloride from the triethylammonium chloride formed. Thus, the use of three equivalents of triethylamine depressed the dissociation of the salt to give allene as the sole product.

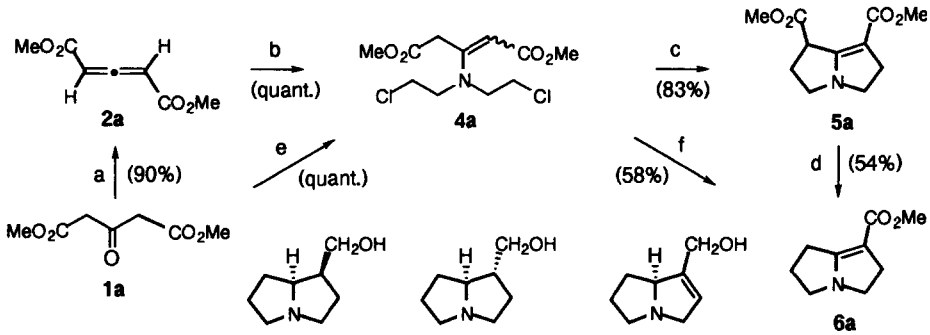
Since allene-1,3-dicarboxylate **2** has extremely high reactivity as a Michael acceptor by the electron-withdrawing effect of the two ester substituents, its reaction with a secondary amide ion as a nucleophile will afford the Michael adduct ion **4**, which can be considered to be a dianion equivalent **A** as illustrated in Scheme 3. We expected that the adduct ion **4** underwent a tandem cyclization to give a series of azabicyclic compound **5**, in the case of secondary amine (R'_2NH) bearing a leaving group in each of two R' groups.

Scheme 3. A Novel Tandem Cyclization to Azabicyclic Compound



Based on the above consideration, we planned to study a facile synthesis of the basic skeleton **6** of a pyrrolizidine alkaloid *via* a novel tandem cyclization using allene **2**, as shown in Scheme 4.

Scheme 4. A Facile Synthesis of Pyrrolizidine Alkaloid Skeleton **6a**



(±)-isoretronecanol (±)-trachelanthamidine (±)-supinidine

a) DMC (1.2 eq.), Et_3N (3 eq.), CH_2Cl_2, r.t. 1 h; b) bis(2-chloroethyl)amine (1.2 eq.), Et_3N (1.2 eq.), benzene, r.t. 12 h; c) NaH (2.2 eq.), DMF, r.t. 8 h; d) 1) LiOH (1 eq.), r.t. 13 h, 2) 2*N*-HCl, r.t. 16 h; e) DMC (1.2 eq.), Et_3N (3 eq.), CH_2Cl_2, r.t. 2 h, then bis(2-chloroethyl)amine (1.5 eq.), r.t. 2 h,; f) NaH (3 eq.), DMF, r.t. 2.5 h; H_2O, r.t. 3 h; 2*N*-HCl, r.t. 9 h

Dimethyl allene-1,3-dicarboxylate (**2a**) reacted with bis(2-chloroethyl)amine to give the Michael adduct **4a** in quantitative yield. A tandem cyclization of the Michael adduct **4a** was performed to give dimethyl ester **5a** bearing a 1-azabicyclo[3.3.0]octane skeleton by the treatment of two equivalents of sodium hydride in 83% yield, accompanied with the mono-cyclized product in 8% yield. Selective hydrolysis of the non-conjugated methyl ester in dimethyl ester **5a** with one equivalent of lithium hydroxide and the subsequent decarboxylation

of the resultant vinylogous half-ester and isomerization of the double bond from β,γ- to the α,β-unsaturated ester with hydrochloric acid afforded the methyl ester **6a**[5] in 54% yield.

Next, we tried simplification of the above procedure. Thus, the adduct **4a** was quantitatively formed in one-pot reaction by the addition of bis(2-chloroethyl)amine into the reaction mixture with keto diester **1a** and DMC in the presence of triethylamine (3 eq.).[6] The methyl ester **6a** was also obtained in one-pot reaction from the Michael adduct **4a** in 58% yield, *i.e.*, the adduct **4a** was treated with sodium hydride (3 eq.) in DMF, then water was added to the reaction mixture for hydrolysis of the non-conjugated methyl ester after the formation of **5a** was confirmed by thin-layer chromatography; finally, the reaction mixture was acidified with 2*N*-hydrochloric acid. The obtained **6a** is useful as a common intermediate for the total syntheses of pyrrolizidine alkaloids,[7] (±)-isoretronecanol, (±)-trachelanthamidine, and (±)-supinidine, because their transformation from its ethyl ester has been accomplished.[8,9] Further studies on the syntheses of optically active pyrrolizidine alkaloids are in progress.

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6. Adduct **4a** was not produced by the dehydration from a mixture of **1a** and bis(2-chloroethyl)amine, nor by the addition of DMC into the mixture.
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