

Practical Synthesis of α, α -Dibromo Esters from Aldehydes

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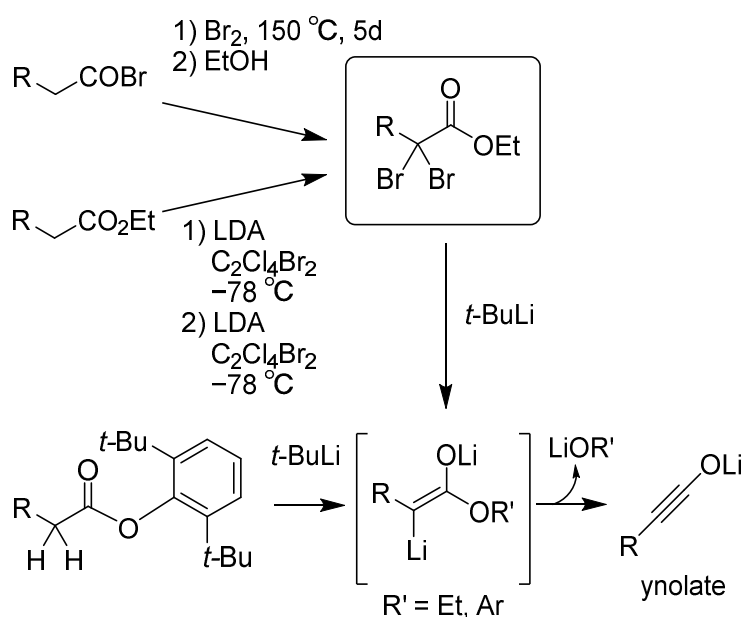
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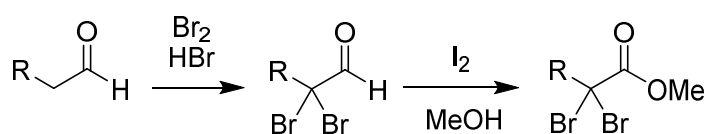
this useful carbanion species will find broader application in organic synthesis. To address this challenge, we recently reported a new method for preparing ynolates based on the double deprotonation of easily prepared nonbrominated 2',6'-di-*tert*-butyl phenyl esters.⁹ In this note, we present an alternative solution and report an efficient method for the preparation of α,α -dibromo esters from aldehydes that are more readily brominated (Scheme 1B).

Generally, esters are not easily prone to enolization; thus, their functionalization at the α -position often requires the formation of enolates using strong bases. In contrast, aldehydes readily undergo enolization under both acidic and basic conditions, and it has been reported that a few α,α -dibromo aldehydes were synthesized from the corresponding aldehyde by treatment with bromine in the presence of an acid catalyst.¹⁰ Therefore, we conceived a two-step method that included the dibromination of aldehydes, followed by oxidative esterification.

A) Previous work

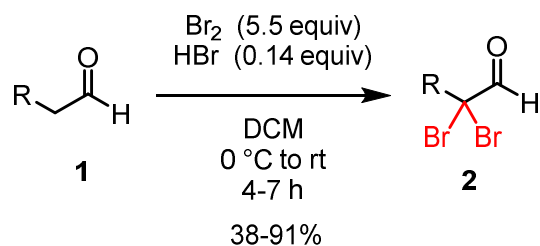


(B) This work



Scheme 1. Preparation of α,α -dibromo esters, precursors of ynolate.

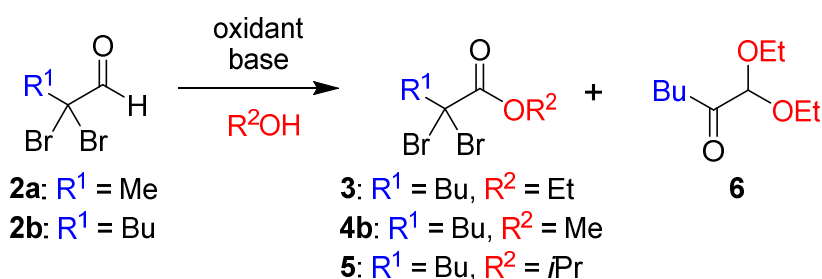
The study began with the dibromination of aldehydes **1** by treatment with bromine in the presence of HBr catalyst, according to the literature¹⁰ (Scheme 2). This reaction proceeded cleanly, affording α,α -dibromo esters **2** in good yield in most cases. However, because α,α -dibromo aldehydes bearing short alkyl groups are highly volatile, their yields were moderate (for details, see supporting information).



Scheme 2. Dibromination of aldehydes.

We then investigated the oxidative esterification of the dibromo esters (Table 1). When Oxone¹¹ was used as the oxidizing reagent, the reaction using **2a** did not proceed (entry 1). Employing CAN in the presence of lithium bromide¹² resulted in the formation of complex mixtures (entry 2). In contrast, the treatment of **2b** with bromine¹³ enabled the desired reaction to proceed slowly, which yielded dibromo ester **3** in 58% yield along with α -ketoacetal **6** in 11% yield (entry 3). The use of iodine¹⁴ accelerated the desired reaction and provided **3** in 71% yield without the formation of ketoacetal **6**. However, based on GC-MS and ¹H NMR analysis, it was found that the product **2a** obtained by this method contained a small amount of iodoform, and its exposure to heat during distillation or light caused the production of iodine, which gave the compound a deep red color. Although the iodoform could be removed to some extent by repeated distillation, the product was not completely purified. As iodoform is derived from the oxidation of ethanol, the solvent converted to methanol. As a result, methyl ester **4b** was obtained in 62% yield. Additionally, when the alcohol was changed to isopropanol, the corresponding ester **5** was obtained in a similar yield. In contrast, when *tert*-butyl alcohol was utilized, the desired product was not obtained, possibly because of the insufficient nucleophilicity caused by steric bulkiness. After considering all observations, we employed the conditions of entry 5 as the optimal conditions for the following experiments.

Table 1. Oxidative esterification of dibromo aldehydes.

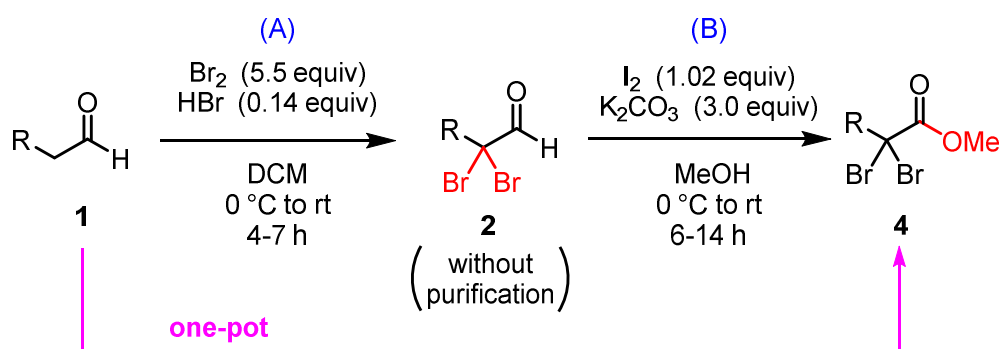


Entry	substrate	Oxidant (equiv)	Base (equiv)	R ²	Temp	Time (h)	Yield
1	2a	Oxone (2)	-	Et	RT to 60°C	22	No reaction
2	2a	CAN (2)	-	Et	RT	4	Complex mixture
		LiBr (0.3)					
3	2b	Br ₂ (6)	NaHCO ₃ (20)	Et	60°C	32	3: 58% 6: 11%
4	2b	I ₂ (1.2)	K ₂ CO ₃ (3)	Et	0°C to RT	12	3: 71% ^a
5	2b	I ₂ (1.2)	K ₂ CO ₃ (3)	Me	0°C to RT	14	4b: 62%
6	2b	I ₂ (1.2)	K ₂ CO ₃ (3)	<i>i</i> -Pr	0°C to RT	7	5: 73%
7	2b	I ₂ (1.2)	K ₂ CO ₃ (3)	<i>t</i> -Bu	RT to 60°C	48	Not obtained

^a Trace amount of iodoform was present.

We then performed a two-step synthesis of dibromo ester **4a** from propanal (**1a**, Table 2, entry 1). After dibromination (step A) was performed, the obtained crude product was used for oxidative esterification without purification (step B). However, as described above, during the workup process in step A, a portion of 2,2-dibromopropanal (**2a**) was lost because of its low boiling point. Therefore, the two-step yield of dibromo ester **4a** was as low as 37%. To improve the efficiency of the synthesis using volatile aldehydes, we performed a one-pot synthesis (entry 2). After step A, the reaction solution was neutralized by treatment with potassium carbonate, and methanol and iodine were added to it directly. The yield of **4a** then improved to 49%. Using this one-pot method, short-chain alkylated dibromo esters **4c,d,b** were synthesized in over 70% yield (entries 3,5,8). In addition, the stepwise method efficiently furnished dibromo esters bearing longer-chain alkyl groups involving propyl to heptyl groups, as well as isopropyl and *tert*-butyl groups (entries 4,6,7,9-12). In entries 7 and 11, this method was scaled up to produce more than 30 grams of dibromo esters. In contrast, in the case of the phenyl group, the second reaction produced multiple products containing the α -ketoester (methyl 2-oxo-2-phenylacetate, 13%), and the yield of the desired dibromo ester **4j** was 23% (entry 13).

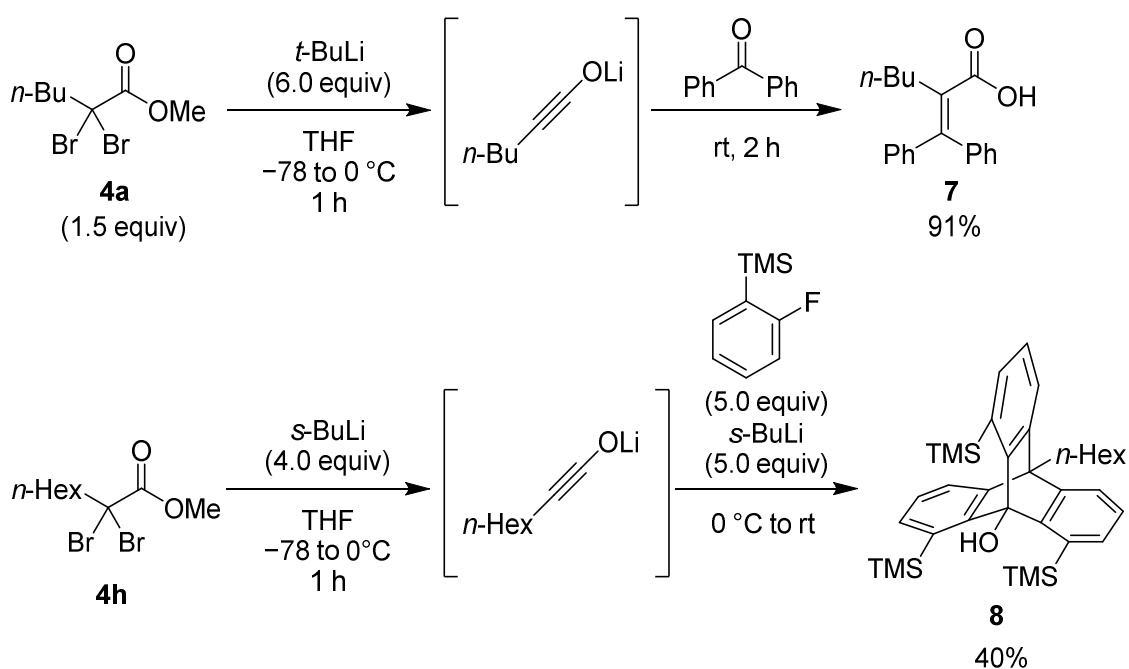
Table 2. Two-step synthesis for α,α -dibromo esters from aldehydes.



Entry	R	Method	Total yield
1	Me	stepwise	37%
2	Me	one-pot	49%
3	Et	one-pot	73%
4	Pr	stepwise	41%
5	Pr	one-pot	71%
6	<i>i</i> -Bu	stepwise	46%
7	<i>n</i> -Bu	stepwise	63% (54% ^a)
8	<i>n</i> -Bu	one-pot	75%
9	<i>t</i> -Bu	stepwise	59%
10	<i>n</i> -Hex	stepwise	64%
11	<i>n</i> -Oct	stepwise	78% (65% ^a)
12	<i>n</i> -Dec	stepwise	68%
13	Ph	stepwise	23% ^b

^aOver 30 grams of dibromoesters were prepared. ^bMethyl 2-oxo-2-phenylacetate was obtained as a byproduct in 12% yield.

In our previous studies, ynolates were primarily prepared from ethyl and phenyl dibromo esters,⁴ and the synthesis of ynolates from methyl dibromo esters had not been investigated. Thus, the methyl dibromo ester **4a** obtained above was treated with *t*-BuLi to produce the ynolate according to the established method (Scheme 3). Confirmation of ynolate generation was achieved via its reaction with benzophenone, which yielded acrylic acid **7** in 91% yield. In addition, ynolate was also prepared from **4h** using *s*-BuLi,^{4c} which is safer to handle than conventional *t*-BuLi. The subsequent reaction of this ynolate with 3-silylbenzynes gave trisilyltripitycene **8** in 40% yield, which is comparable to our previous report.^{7b}



Scheme 3. Preparation and reactions of ynolates from methyl α,α -dibromo esters.

In summary, we have developed an efficient and practical method for synthesizing α,α -dibromo esters, which are the precursors to ynolates, through the dibromination of aldehydes followed by oxidative esterification using iodine as the oxidant. The method was successfully employed in the scale-up synthesis of more than 30 grams of dibromo esters. Moreover, it is possible to perform these two steps in a one-pot manner, making them adaptable even for aldehydes with low boiling points. We confirmed the efficient generation of ynolates from the obtained methyl dibromo esters by using them in olefination and triptycene synthesis. This method effectively addressed the problem of precursor preparation, which has been a bottleneck in ynolate chemistry, and is expected to contribute to accelerating the use of ynolates in organic synthesis.

ASSOCIATED CONTENT:

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://>

Experimental procedures, compounds data, NMR spectra (PDF)

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