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Practical synthesis of ynolate anions: naphthalene-catalyzed reductive lithiation of α,α-dibromo esters

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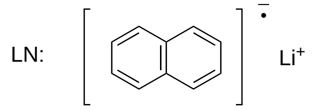
Abstract—Reductive lithiation of α,α-dibromo esters using lithium naphthalenide afforded ester dianions leading to ynolate anions in good yields. Naphthalene-catalyzed reductive lithiation was also accomplished. This is a convenient, economical and practical method for the preparation of ynolate anions. © 2001 Elsevier Science Ltd. All rights reserved.

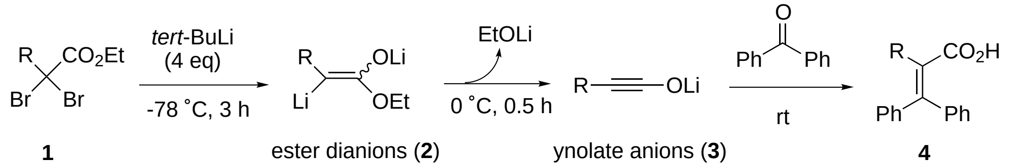
Ynolate anions (**3**) act not only as carbanions forming a carbon–carbon bond but also as ketene anion equivalents.[1] They are therefore expected to undergo unique reaction sequences; however, because of the difficulty of their preparation,[1] their chemistry has not been extensively studied. We have developed a novel methodology for the generation of ynolate anions via cleavage of ester dianions (**2**) prepared from readily available α,α-dibromo esters (**1**) (Scheme 1),[2] and have demonstrated their use as multifunctional carbanions.[3] Although this synthetic method is simple and convenient, the *tert*-butyllithium used in the lithium–halogen exchange is somewhat expensive and should be carefully handled. If a safer and more economical method could be developed, it would be useful, especially for large scale reactions. In this communication, we describe a practical synthesis of ynolate anions, utilizing the naphthalene-catalyzed reductive lithiation of α,α-dibromo esters.

Reductive lithiation of alkyl halides via radical anions[4] is an important method for the preparation of alkyllithium compounds as well as lithium–halogen exchange via *n*- or *tert*-butyllithium.[5] One of the most frequently used arene species in the preparation of the radical anion is naphthalene.[6] To evaluate the efficiency of the generation of lithium ynolates, olefination of benzophenone was selected, since this reaction is known to afford the olefin (**4**) in excellent yields.[3a,3f]

In the first trial, a deep green THF solution (0.4 M) of lithium naphthalenide (LN), prepared by lithium metal and an equimolar amount of naphthalene in THF at room temperature, was added dropwise via syringe to a colorless THF solution of the dibromo ester (**1a**) at −78°C.



After the LN solution (8.3 mL, ca. 3.3 equiv.) was added dropwise over 15 min, the reaction mixture turned deep green. At this stage, **1a** was completely



Scheme 1.

Keywords: ynolate anion; radical anion; catalytic reductive lithiation; lithium naphthalenide.

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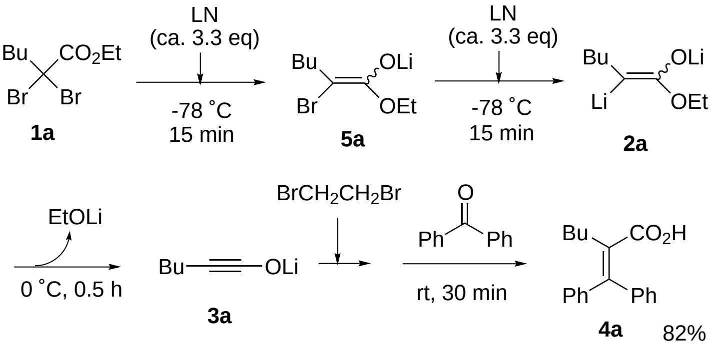
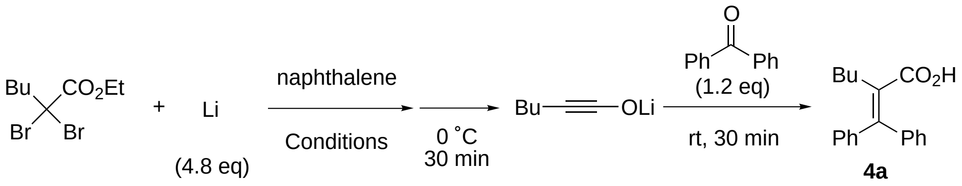
converted into the monoanion (**5a**).[†] The same amount (8.3 mL, ca. 3.3 equiv.) of LN solution was added dropwise over 15 min at −78°C. The deep green reaction mixture was then warmed to 0°C and was stirred for 30 min. After addition of several drops (ca 0.18 equiv.) of 1,2-dibromoethane to quench the excess radical anion, a THF solution of benzophenone (1.2 equiv. based on the dibromo ester)[‡] was added at room temperature. The mixture was stirred for an additional 30 min before work-up. The desired olefin (**4a**) was isolated in 82% yield, demonstrating that the ynolate anion (**3a**) was generated in good yield via the radical anion method. It also illustrates that the first lithiation furnishing **5a** was very fast while the second giving the dianion (**2a**) was relatively slow. In this method, an excess of LN was required, probably due to air contamination during the transfer of the LN solution via syringe (Scheme 2).

Next, we examined the addition of α,α-dibromo ester to the LN solution (Scheme 3). To the LN solution (ca. 4.8 mmol) was added the dibromo ester (1.0 mmol) at −78°C. After stirring for 30 min, the reaction was allowed to warm to 0°C and was stirred for an additional 30 min. After addition of 1,2-dibromoethane, benzophenone (1.2 mmol) was added at room temperature. The desired olefin (**4a**) was isolated in 84% yield (Table 1, entry 1). In both methods, the efficiency of generation of ynolates is extremely high. However, more than 5 equiv. of naphthalene must be removed after the reaction, although it can be recovered.

To solve this problem, naphthalene-catalyzed reductive lithiation[7] of α,α-dibromo esters was examined (Table 1). Using 42 mol% (based on lithium) of naphthalene, the reaction gave **4a** in 72% yield, although it took 3.5



Scheme 2.



Scheme 3.

Table 1. Naphthalene-catalyzed reductive lithiation of α,α-dibromo esters leading to ynolate anions

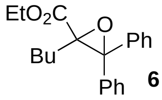
Entry	Naphthalene (mol%)[a]	Preparation time of LN (min)[b]	Conditions	Yield (%)[c]
1	104	80	−78°C, 30 min	84
2	42	40	−78°C, 3.5 h	72
3	21	15	−78°C, 20 min; −50°C, 2.0 h	73
4	21	15	−50°C, 2 h	65
5	10	15	−78°C, 40 min; −50°C, 2.5 h	78
6	5	15	−78°C, 30 min; −50°C, 4 h	79
7	2.6	15	−78°C, 1.5 h; −50°C, 7.5 h	68

[a] Based on lithium metal.

[b] Lithium (4.8 mmol) and naphthalene in THF (13 mL) were stirred at room temperature.

[c] Based on dibromo ester.

[†] At this stage, Darzen's product (**6**) was isolated if the reaction mixture was treated with benzophenone at room temperature.



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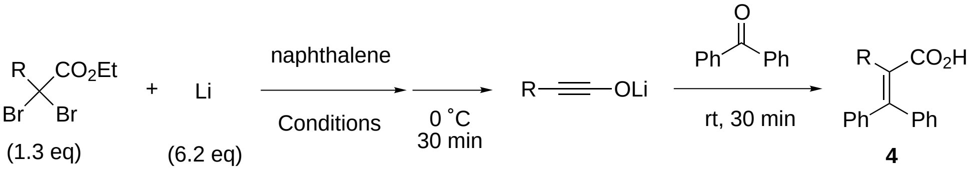
[‡] To estimate the efficiency of the synthesis, a small excess of the electrophile was used.



Scheme 4.

Table 2. Olefination of benzophenone via ynolate anions generated by catalytic reductive lithiation[a]

Entry	R	Conditions	Yield (%)
1	Me	−78°C, 45 min; −50°C, 3 h	89
2[b]	Me	−78°C, 50 min; −50°C, 3 h	78[c]
3	Bu	−78°C, 30 min; −50°C, 3 h	89
4	*i*Pr	−78°C, 25 min; −50°C, 3 h	99
5	$PhCH_2CH_2$	−78°C, 30 min; −50°C, 3 h	94
6	*tert*-Bu	−78°C, 15 min; −50°C, 3 h	85
7	Ph	−78°C, 25 min; −50°C, 3 h	72
8	Ph	−100°C, 1.5 h; −78°C, 3 h	94

[a] Unless otherwise noted, 1 mmol of benzophenone was employed. In all cases, 10 mol% of naphthalene was used. The typical procedure was described in Ref. 8.

[b] 10 mmol scale.

[c] Benzophenone was recovered in 19%.

h to complete the reductive lithiation (entry 2). Encouraged by these results, we continued to search for the optimum conditions for more efficient catalytic reactions. When 21 mol% of naphthalene was used, the colorless reaction mixture changed to deep green at −78°C. The change in color indicated the completion of the first lithiation. After the reaction mixture stirred at −50°C for 2 h, the desired product was obtained in 73% yield (entry 3). However, the reaction, which was carried out at −50°C from the beginning, gave lower yields (entry 4), probably due to undesired reactions between the unreacted dibromo ester (**1a**) and the lithium enolate **5a**. Satisfactory yields were successfully obtained in the range of 2.6–10 mol% of naphthalene (entries 5–7). Thus, the naphthalene-catalyzed reductive lithiation of dibromo esters leading to the practical synthesis of ynolate anions was successful.

To examine the generality of this process, several kinds of ynolate anions were synthesized (Scheme 4, Table 2). In these reactions, a slight excess of ynolate anions to benzophenone was used. As shown in Table 2, alkyl-substituted ynolate anions were efficiently synthesized to afford the desired olefins (**4**) in excellent yields (entries 1–6).[8] The reaction on a 10 mmol scale also afforded the product in good yield (entry 2), demonstrating that this method is suitable for large scale reactions. In the case of the phenyl substituted ynolate anion, only a moderate yield was obtained (entry 7), while at lower temperatures, the yield was improved to 94%, as shown in entry 8.

This process was applied to the tandem reaction which we developed. The tandem [2+2] cycloaddition–Dieckmann condensation[3c] afforded the cyclohexenone (**7**) in excellent yield (Scheme 5).

In conclusion, we have developed a highly efficient synthetic method for the generation of ynolate anions via naphthalene-catalyzed reductive lithiation of α,α-dibromo esters. Compared with the previous methods, ours is not only safe and economical, but also general and convenient, allowing advances and wide use of ynolate anions.

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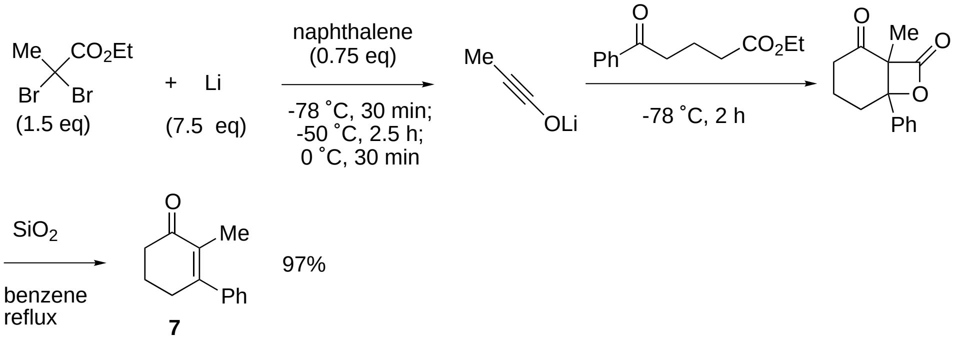

Scheme 5.

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8. Typical procedure: To the LN solution, prepared by reaction of naphthalene (0.65 mmol) and lithium (6.2 mmol) in THF (13 mL) for 15 min, was added a THF solution (2 mL) of the dibromo ester (1.0 mmol) at −78°C. After stirring for 45 min at −78°C and for 3 h at −50°C, the reaction was allowed to warm to 0°C and was stirred for an additional 30 min. After the addition of 1,2-dibromoethane (ca. 0.15 mmol), benzophenone (1.0 mmol) was added at room temperature. The solution was stirred again for 30 min before work-up. The reaction was diluted with ether and extracted with aqueous NaOH solution. The aqueous layer was then acidified and extracted with ether. The organic layer was concentrated to afford the almost pure product.