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An Efficient Protocol for the Preparation of Ynones from Esters and Acid Chlorides

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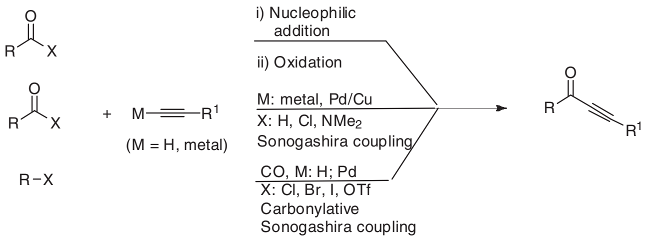
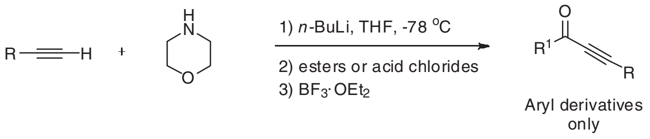
Ynones (α,β-acetylenic ketones) are important structural motifs that are widely distributed in bioactive natural products.[1] The synthesis of ynones is a hot topic of research owing to their potential utility as versatile building blocks for several organic molecules and other materials.[2] In general, ynones are prepared by the addition of acetylides to carbonyl compounds, followed by oxidation,[3] metal-catalyzed Sonogashira coupling of terminal alkynes to carbonyl derivatives, and carbonylative Sonogashira coupling of alkynes to aryl halides and triflates in presence of carbon monoxide[4,5] (Scheme 1). However, the reported methods often involve the use of toxic and expensive metals and ligands. Recently, transition-metal-free synthesis of ynones has been attempted with the aim of making the process less hazardous.[6] Despite such significant efforts, the development of an efficient and robust method toward the synthesis of this valuable intermediate is of continuous interest in organic synthesis.

As part of our ongoing research, we recently reported the synthesis of ynones by the nucleophilic addition of lithium acetylide to acetyl chlorides and esters in presence of $BF_3 \cdot OEt_2$ at −78 °C (Scheme 2).[7]

Based on previous experience and literature reports,[8] we herein report the preparation of ynones by a modified and efficient protocol under ambient temperature, without the use of any Lewis acid.



Scheme 1. Methods for preparation of ynones.

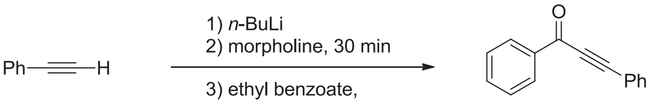


Scheme 2. Synthesis of ynones from esters and acid chlorides.

Our initial attempts were directed toward the synthesis of ynones from ester moieties. A model reaction of phenyl acetylene with ethyl benzoate was selected for optimization of the reaction parameters such as mole ratios of phenyl acetylide and morpholine, temperature, and reaction time. The results are listed in Table 1.

When the reaction was performed at 0 °C with 4.0 equiv of lithium phenyl acetylide, partial alknylation of ethyl benzoate occurred to furnish the ynone in reasonable yield (67%), along with the amide (entry 1). The ynone yield increased (86%) with an increase in the reaction time (entry 3), and no starting ester was detected under these conditions. However, a similar reaction at room temperature led to a decreased rate of ynone formation (entries 4–5). The change in the mole ratio of morpholine had no significant effect on the ynone conversion (entries 6–8). From the experimental data, the optimized conditions for the partial alkynylation of carbonyl esters in this system were established as follows: 1.1 equiv morpholine; 4.0 equiv lithium phenyl acetylide; 0 °C.

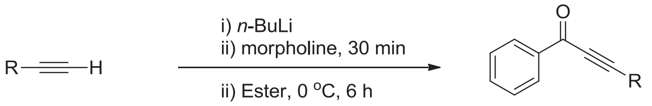
Table 1. Optimization of reaction conditions for synthesis of ynone from ethyl benzoate.

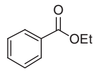
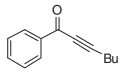
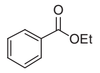
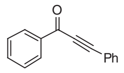
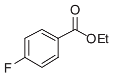
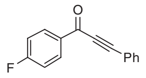
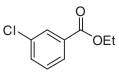
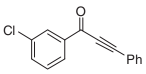
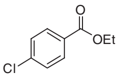
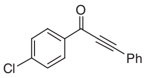
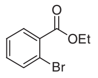
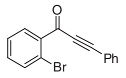
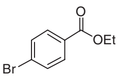
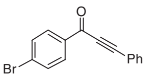
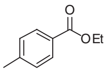
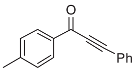
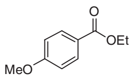
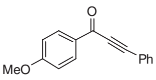
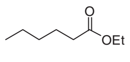
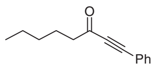
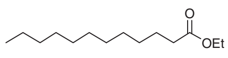
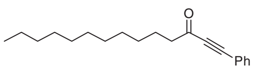
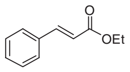
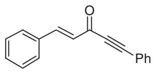


Entry	Morpholine (equiv)	Lithium phenyl cetylide (equiv)	Temp.	Time (h)	Yield of ynone[a]
1	1.1	4.0	0 °C	1	67
2				3	79
3				6	86
4	1.1	4.0	rt	3	79
5				6	64
6	2.1	4.0	0 °C	6	81
7	3.1	4.0		6	58
8	4.1	4.0		6	44

[a] Yields were determined by gas chromatography.

Table 2. Yields of ynone from representative esters.[a]

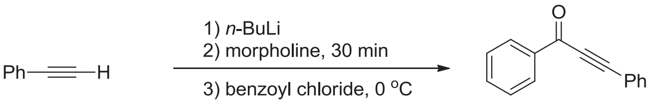


Entry	Ester	R	Product	Yield (%)[b]
1		Bu		83
2		Ph		85
3				77
4				73
5				87
6				73
7				76
8				81
9				78
10				39
11				48
12				82

[a] Morpholine : Phenylacetylene : Ester = 1.1:4.0:1.0.
[b] Isolated yields after silica column chromatography.

With the optimized reaction conditions for the ester functionality in hand, we explored the efficiency of this condition by examining the various carboxylic esters. As shown in Table 2, various esters with electron-withdrawing and electron-donating substituents smoothly underwent conversion to the corresponding ynones in good yields (73–87%; entries 1–9). However, aliphatic esters afforded lower yields (39–48%) of ynones (entries 10–11) under the reaction conditions. Generally, carboxylic esters participate to a lesser extent in the partial alkynylation due to possible over-addition reactions. Furthermore, ethyl cinnamate, an α,β-unsaturated ester, gave 82% yield of cinnamaldehyde (entry 12). Hence, acyl chlorides are often utilized for this transformation considering the change in reactivity.

Table 3. Optimization of reaction conditions for synthesis of ynone from benzoyl chloride.



Entry	Morpholine (equiv)	Lithium phenyl acetylide (equiv)	Time (min)	Yield (%)[a]
1	1.0	2.0	30	64
2		4.0	30	83
3	1.5	4.0	10	93
4			30	94
5	2.0	4.0	10	96

[a] Yields were determined by gas chromatography.

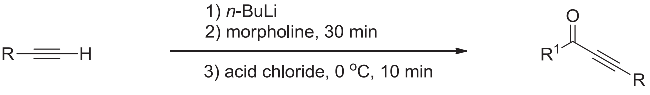
We then optimized the conditions for ynone synthesis from acyl chlorides by considering the difference between the reactivity of acyl chlorides and esters toward nucleophilic acetylide addition (Table 3). Accordingly, a model reaction involving the treatment of benzoyl chloride with phenyl acetylide was carried out. A moderate yield (64%) of the ynone was obtained with 2.0 equiv of lithium phenyl acetylide within 30 min (entry 1). A change in the mole ratio of phenyl acetylide from 2.0 to 4.0 equiv increased the yield of the desired ynone to 83% (entry 2). A slight increase in the morpholine mole ratio led to a high yield of the ynone (93%) in a short time (entry 3). However, with a further increase in the morpholine ratio, there was no notable difference in the product yield (entries 4–5).

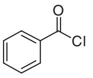
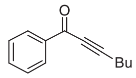
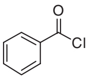
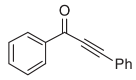
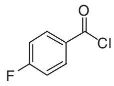
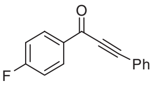
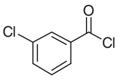
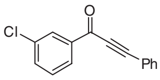
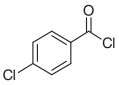
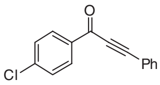
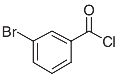
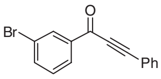
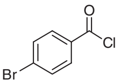
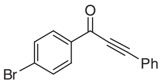
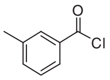
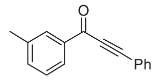
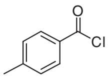
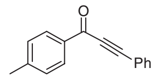
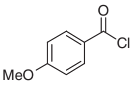
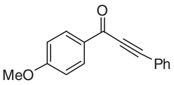
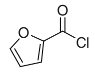
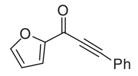
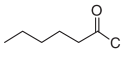
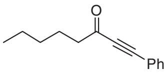
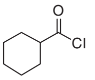
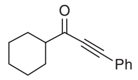
It was demonstrated that because of the equilibrium between lithium acetylide and morpholine amide (generated *in situ*), a slight excess of the reagent is necessary to promote this transformation with good conversion.[3c]

Next, various acid chlorides with aromatic, heteroaromatic, and aliphatic functionalities were subjected to the optimized reaction conditions to furnish the corresponding ynones (Table 4). Most of the derivatives having electron-rich and electron-deficient substituents smoothly underwent this transformation and afforded ynones in good to excellent yields (72–96%; entries 1–10). A heteroaromatic acid chloride, furan-2-carbonyl chloride, also furnished the corresponding ynone in 82% yield (entry 11). Aliphatic acid chlorides furnished the corresponding ynones in the presence of 3.0 equiv morpholine and 8.0 equiv phenyl acetylide with respect to the starting compound (entries 12–13).

A plausible mechanism for the ynone synthesis from acid chloride is presented in Scheme 3. Lithium phenyl acetylide generated by the reaction with *n*-BuLi first reacts with morpholine to form lithium morpholide. The reaction of this lithium morpholide with benzoyl chloride and subsequent elimination of LiCl would lead to the formation of a stable morpholine amide.[7b] The amide reacts with lithium phenyl acetylide (present in the reaction mixture) to afford a propargylic alcohol complex by coordination with lithium through a stable seven-membered transition state. Subsequent quenching of this intermediate would furnish the desired ynone (Scheme 3).

Table 4. Yields of ynones from representative acid chlorides.[a]

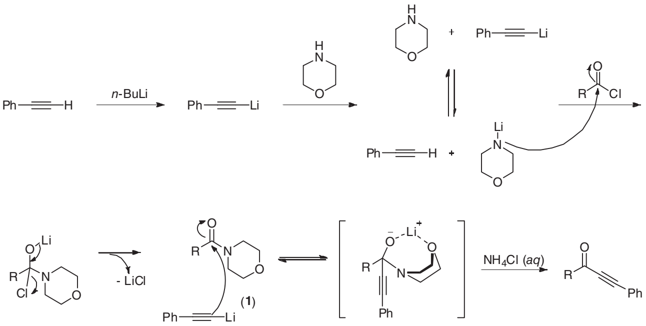


Entry	R	Acid chloride	Product	Isolated yield (%)
1	Bu			91
2	Ph			86
3				84
4				88
5				96
6	Ph			91
7				95
8				96
9				86
10				72
11				82
12[b]				59 (86)[c]
13[b]				57

[a] Acetylide anion : n-BuLi : morpholine : acid chloride = 4.1:4.0:1.5:1.0.

[b] Acetylide anion : n-BuLi : morpholine : acid chloride = 8.1:8.0:3.0:1.0.

[c] Yield was determined by gas chromatography.



Scheme 3. Proposed mechanism for ynone synthesis from acid chloride.

In summary, we have identified a simple and efficient synthesis route to ynones via the partial alkynylation of carbonyl derivatives such as esters and acid chlorides in the presence of lithium phenyl acetylide and morpholine. This method affords ynones in good to excellent yields starting from various esters and acid chlorides. The *in situ* generation of morpholine amide, non-requirement of Lewis acids, and ambient reaction conditions make this system suitable for ynone synthesis from commercially available reagents.

Experimental

General. All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out using standard techniques for the handling of air-sensitive materials. All chemicals were commercial products of the highest purity, which were further purified before use by using standard methods. THF was dried over sodiumbenzophenone and distilled. n-butyllithium, esters, aldehydes, and morpholine were purchased from Aldrich Chemical Company (St. Louis, MO, USA), Alfa Aesar (Milwaukee, WI, USA), and Tokyo Chemical Industry Company (TCI, Tokyo, Japan). ^{1}H NMR spectra were measured at 300 or 400 MHz with $CDCl_3$ as a solvent at ambient temperature unless otherwise indicated and the chemical shifts were recorded in parts per million downfield from tetramethylsilane (0 ppm) or based on residual $CHCl_3$ (7.26 ppm) as an internal standard. ^{13}C NMR spectra were recorded at 75 or 100 MHz with $CDCl_3$ as a solvent and referenced to the central line of the solvent (77.0 ppm). The coupling constants (J) are reported in Hertz. Analytical thin-layer chromatography (TLC) was performed on glass precoated with silica gel (silica gel 60 F_{254}, Merck, Darmstadt, Germany). Column chromatography was carried out using 70–230 mesh silica gel (Merck) at normal pressure. Gas chromatography analyses were performed on a Younglin Acme 6000 M (Younglin, Anyang, Gyeonggi-do, South Korea) and 6100GC FID (Younglin, Anyang, Gyeonggi-do, South Korea) chromatography, using an HP-5 (Agilent Technologies, Santa clara, CA, USA) capillary column (30 m). All GC yields were determined with the use of naphthalene as internal standard and authentic mixture.

Partial Alkynylation of Esters to Corresponding Ynones. The following experimental procedure for the partial alkynylation of ethyl benzoate to 1,3-diphenylprop-2-yn-1-one is representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with phenyl acetylene (0.45 mL, 4.1 mmol) and THF (10 mL). After cooling to 0 °C, *n*-BuLi (1.6 mL, 2.5 M in hexane, 4.0 mmol) was added dropwise and stirred for 1 h at room temperature. To the reaction mixture was slowly added morpholine (0.08 mL, 1.0 mmol) and stirred for 30 min at 0 °C. Then, ethyl benzoate (0.14 mL, 1.0 mmol) was added and the mixture was stirred for 6 h again. The reaction was stopped by aqueous NH_4Cl (aq) (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel yielded 1,3-diphenylprop-2-yn-1-one (175 mg, 85%). All products in Table 2 were confirmed by comparison with NMR data reported of authentic sample.[7]

Partial Alkynylation of Acid Chlorides to Corresponding Ynones. The following experimental procedure for the partial alkynylation of benzoyl chloride to 1,3-diphenylprop-2-yn-1-one is representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with phenyl acetylene (0.45 mL, 4.1 mmol) and 10 mL THF. After cooling to 0 °C, *n*-BuLi (1.6 mL, 2.5 M in hexane, 4.0 mmol) was added dropwise and stirred for 1 h at room temperature. To the reaction mixture was slowly added morpholine (0.13 mL, 1.5 mmol) and stirred for 30 min at 0 °C. Then, benzoyl chloride (0.13 mL, 1.0 mmol) was added and the mixture was stirred for 10 min again. The reaction was stopped by aqueous NH_4Cl (aq) (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$. GC analysis showed a 86% yield of 1,3-diphenylprop-2-yn-1-one. All products in Table 4 were confirmed by comparison with NMR data reported of authentic sample.[7]

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