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A new and efficient one-pot synthesis of aromatic alkynyl ketones from aromatic esters

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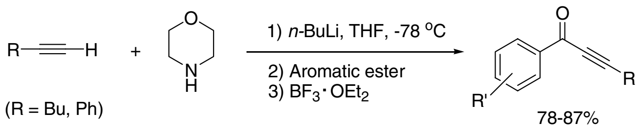
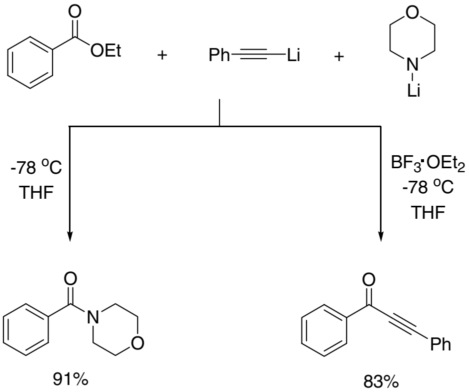
Abstract—The reaction of aromatic esters with alkynyllithiums in the presence of lithium morpholinide and $BF_3·OEt_2$ gave aromatic alkynyl ketones in good yield (78–87%).

Alkynyl ketones are valuable intermediates widely used in organic synthesis. α,β-Acetylenic carbonyl compounds can, for example, undergo sequential nucleophilic additions and cyclizations, leading to various heterocyclic derivatives.[1] They can also serve as intermediates for the synthesis of natural products,[2] heterocyclic ligands or precursors for materials with interesting properties. Furthermore, the one-pot process has recently gained a considerable and steadily increasing academic, economic and ecological interest because it addresses very fundamental principles of organic synthesis efficiency and reaction design. A variety of synthetic approaches to alkynyl ketones have been reported. Among them, palladium- and/or copper-catalyzed cross-couplings of terminal acetylenic derivatives with acid chlorides are usually considered to be the methods of choice.[3] On the other hand, in the case of esters, the preparation of the alkynyl ketones proceeds via addition reaction using metal acetylides such as alkynyl lithium[4] or alkynyl lithium with $BF_3·OEt_2$.[5] This addition reaction could be one of the convenient ways to synthesize alkynyl ketones. However, these methods gave great problems in that the use of esters was limited to aliphatic esters because of the formation of tertiary alcohol or lack of reaction in the alkynylation of aromatic esters. Herein, we wish to report a new and efficient synthetic method for synthesizing aromatic alkynyl ketones which is based on partial alkynylation of aromatic esters by using lithium morpholinide and alkynyl lithiums prepared from morpholine and alkyne by *n*-butyllithium with $BF_3·OEt_2$ (Scheme 1).[6]



Scheme 1.

Recently, we investigated the reaction of ethyl benzoate by treatment with a lithium morpholinide and phenylacetylenic lithium at −78 °C, which afforded the corresponding amide in 91% yield. On the other hand, when $BF_3·OEt_2$ as Lewis acid was added to the reaction mixture under the same reaction conditions, the reaction afforded the corresponding aromatic alkynyl ketone in 83% yield. This result suggests that the lithium morpholinide was more reactive than alkynyl lithium to aromatic esters at −78 °C (Scheme 2).



Scheme 2.

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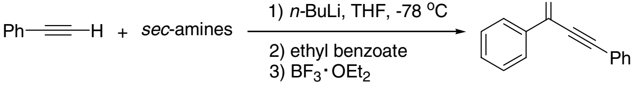
Table 1. Partial alkynylation of ethyl benzoate in the presence of various secondary amines[a]



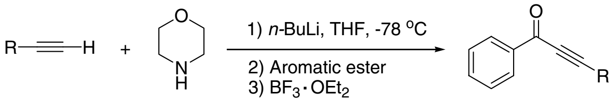
Entry	*sec*-Amines	Isolated yield (%)
1	Diethylamine	0
2	Dihexylamine	67
3	Dicyclohexylamine	0
4	Piperidine	62
5	Morpholine	83
6	Pyrrolidine	7
7	Pyrrole	0
8	Indole	0

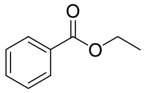
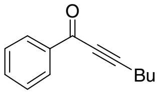
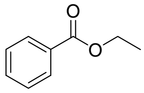
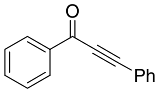
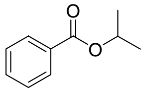
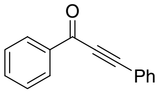
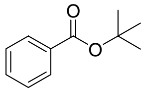
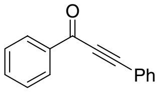
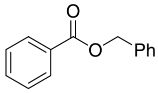
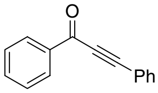
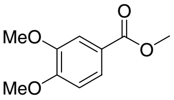
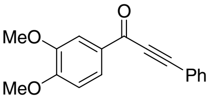
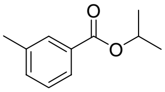
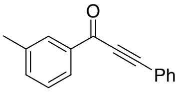
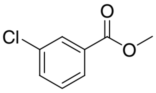
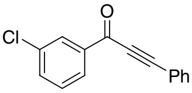
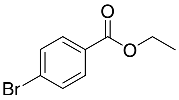
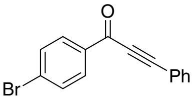
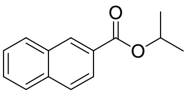
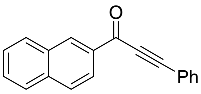
[a] Ethyl benzoate:phenyl acetylene:amine:*n*-BuLi:$BF_3{\cdot}OEt_2$ = 1:3:1:4:1.

Next, as shown in Table 1, we examined partial alkynylation of aromatic esters to aromatic alkynyl ketones by using various secondary amines such as diethylamine, dihexylamine, dicyclohexylamine, piperidine, pyrrolidine, pyrrole and indole. Among those examined, we could not find better results than those with morpholine.

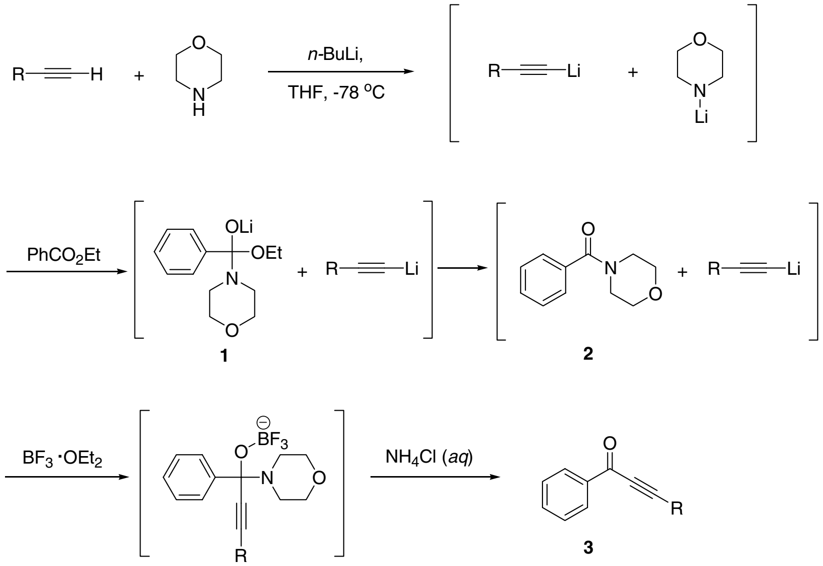
With these results in hand, we anticipated that treatment of aromatic esters with lithium morpholinide and alkynyl lithiums in the presence of $BF_3{\cdot}OEt_2$ might open up a one-pot access to aromatic alkynyl ketones. Table 2 summarizes the results of successive treatment of representative aromatic esters. As shown in Table 2, aromatic alkynyl ketones can be readily synthesized from ethyl, isopropyl, *t*-butyl and benzyl benzoate in 80–87% yield (entries 2–5). Noteworthy also is the fact that, since

Table 2. Yields of aromatic alkynyl ketones in the partial acetylation of representative aromatic esters[a]



Entry	R	Ester	Product	Isolated yield (%)
1	Bu			82
2	Ph			83
3				80
4				81
5				87
6				87
7				84
8				78
9				81
10				82

[a] Ester:acetylene:morpholine:*n*-BuLi:$BF_3{\cdot}OEt_2$ = 1:3:1:4:1.



Scheme 3.

these kinds of alkyne can tolerate the reaction with various aromatic esters, the reaction opens up an easy access to aromatic alkynyl ketones containing aromatic and aliphatic alkynes (entries 1 and 2). Also, benzoates with an electron-donating substituents such as methyl 3,4-dimethoxybenzoate and isopropyl 3-methylbenzoate, and electron withdrawing substituents such as methyl 3-chlorobenzoate and ethyl 4-bromobenzoate were readily produced to the corresponding aromatic alkynyl ketones in 78–87% yields (entries 6–9). Similarly, isopropyl naphthoate, a poly-aromatic ester, gave the corresponding alkynyl ketone in 82% yield (entry 10).

A proposed mechanism of this reaction is shown in (Scheme 3). Reaction of equimolar ethyl benzoate and lithium morpholinide rapidly forms stable intermediate **1** by attack of the morpholinyl group on sp^2 carbon of the ester, and this is quickly transformed into a more stable intermediate, amide **2**. The resulting amide **2** was then reacted with $BF_3{\cdot}OEt_2$ as Lewis acid and alkynyl lithium at −78 °C to afford the aromatic alkynyl ketone **3** in good yield.

In summary, a one-pot method for synthesizing aromatic alkynyl ketones from aromatic esters has been developed. Thus, it now becomes possible to synthesize not only aliphatic alkynyl ketones but also aromatic alkynyl ketones from esters in good yield (78–87%).

Acknowledgement

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6. The following experimental procedure for the synthesis of 1,3-diphenyl-2-propyn-1-one is representative. To a solution of morpholine (0.09 mL, 1.0 mmol) and phenylacetylene (0.33 mL, 3.0 mmol) in THF (5 mL) was slowly added *n*-butyllithium (6.4 mL, 2.5 M in hexane, 4 mmol) at −78 °C. Stirring was continued for 10 min at −78 °C; to this was added ethyl benzoate (0.14 mL, 1 mmol) and the mixture was stirred for 10 min at the same temperature. To this was added dropwise $BF_3{\cdot}OEt_2$ (0.13 mL, 1 mmol). After being stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The residue was purified by column chromatography on silica gel in the presence of Et_3N.