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Metal-Free Synthesis of Ynones from Acyl Chlorides and Potassium Alkynyltrifluoroborate Salts

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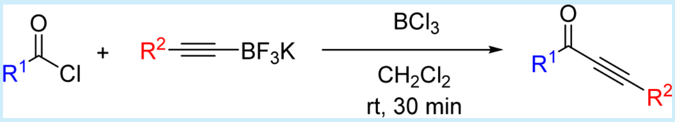
Supporting Information



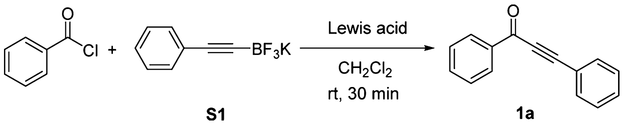
ABSTRACT: A straightforward method for the preparation of ynones from acyl chlorides and potassium alkynyltrifluoroborate salts has been developed. The one-pot reaction proceeds rapidly in the presence of a Lewis acid without exclusion of air and moisture.

Ynones are important building blocks in organic chemistry that have been shown to have biomedical and material significance.[1] In addition, they are precursors to valuable organic functional groups such as pyrimidines,[2] quinolones,[3] furans,[4] pyrazoles,[5] flavones,[6] oximes,[7] and chiral propargylic alcohols.[8] A common route to prepare ynones involves the reaction of metal[9] and metalloid[10] acetylides with acid chlorides. Alternatively, the synthesis of ynones from acyl chlorides can be achieved via two-step procedures using Weinreb amides and organolithium or Grignard reagents.[11] Another common approach includes the addition of organolithium or Grignard reagents to an aldehyde, which is followed by the oxidation of a secondary alcohol to the corresponding ketone.[12] The necessity of purifying synthetic intermediates after each step and poor functional group tolerance of metal acetylides are main deficiencies of the aforementioned methods. Therefore, the utility of ynones as synthetic building blocks highlights the attractiveness of a more straightforward method. More recently, transition-metal-catalyzed carbonylative couplings for the preparation of ynones have emerged as an alternative approach.[13] However, in addition to cost and toxicity associated with transition metals, metal-catalyzed carbonylative reactions often require elevated CO pressures and suffer from the presence of an undesired Sonogashira coupling byproduct.

Our research program is focused on the investigation of transition-metal-free reactions of organoboranes. Therefore, we sought to develop a novel method for the preparation of ynones from acyl chlorides and alkynyltrifluoroborate salts. Potassium organotrifluoroborate salts have recently emerged as versatile reagents in organic synthesis. Their ease of preparation, inherent stability, functional group tolerance, and low toxicity have made trifluoroborates attractive reagents.[14] Organotrifluoroborate salts have long been considered a bench-stable equivalent of boronic acids for palladium-catalyzed Suzuki–Miyaura coupling.[15] Following a seminal work by Matteson and co-workers,[16] Bode, Molander, and others have highlighted the utility of organotrifluorborates as reagents in nonmetal-catalyzed reactions.[17] However, the field of transition-metal-free reactions of trifluoroborates is still in its infancy stage.

Our initial efforts were focused around the preparation of ynone **1a** from phenylacetylenetrifluoroborate **S1** and benzoyl chloride. Several Lewis acids were screened in an effort to find an effective catalyst (Table 1). First, Lewis acids known to react

Table 1. Optimization of Conditions for the Preparation of Ynone 1a[a]



entry	Lewis acid	Lewis acid (equiv)	conditions	yield (%)
1[b]	SiO_2	16.5	CH_2Cl_2	0
2	$SiCl_4$	1.0	CH_2Cl_2	trace
3	$BF_3\cdot OEt_2$	1.0	CH_2Cl_2	trace
4[b]	$FeCl_3$	1.0	CH_2Cl_2	24
5[c]	$AlCl_3$	1.0	CH_2Cl_2	62
6[d]	$AlCl_3$	1.0	CH_2Cl_2	66
7[e]	$AlCl_3$	1.0	CH_2Cl_2	60
8	$AlCl_3$	1.0	THF	trace
9	$AlCl_3$	1.0	toluene	trace
10	$AlCl_3$	2.0	$ClCH_2CH_2Cl$	33
11	$AlCl_3$	1.0	DMSO	trace
12	$AlCl_3$	2.0	acetonitrile	trace
13	$AlCl_3\cdot 6H_2O$	1.0	CH_2Cl_2	0
14[b]	BCl_3	1.5	CH_2Cl_2	67
15	BBr_3	1.0	CH_2Cl_2	20

[a] Reactions were run with 1 equiv of benzoyl chloride and 1 equiv of potassium phenylacetylenetrifluoroborate **S1**. [b] 1.5 equiv of **S1**. [c] Anhydrous conditions. [d] The reaction was done in nondried glassware under air. [e] Anhydrous conditions + 1 μL of water.

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with trifluoroborate salts have been explored. Silica gel,[18] silicon tetrachloride,[15] and boron trifluoride[17c,e] have been reported to convert organotrifluoroborates to organodihaloboranes. Unfortunately, their addition did not promote the formation of the desired ynone (Table 1, entries 1−3). Product **1a** was obtained in low yield when an iron(III) chloride catalyst was employed (Table 1, entry 4). Next, aluminum(III) chloride was investigated due to its well-established ability to promote oxocarbenium ion formation in Friedel−Crafts acylations.[19] We were pleased to obtain the desired product in 62% yield for the $AlCl_3$-catalyzed reaction (Table 1, entry 5).

A slightly elevated yield was obtained when the reaction was performed in the presence of air with glassware that was not dried beforehand (Table 1, entry 6). The addition of a controlled amount of water to the reaction mixture did not improve the yield (Table 1, entry 7). Once it became evident that the reaction could tolerate air and moisture, subsequent reactions (Table 1, entries 8−15) were done in nondried glassware under air. Further attempts to optimize the solvent revealed that dichloromethane (CH_2Cl_2) is particularly well suited to the reaction. Aprotic solvents including THF, toluene, and dichloroethane as well as polar solvents DMSO and acetonitrile were tested with little success (Table 1, entries 8−12).

Unfortunately, inconsistencies in the results of the aluminum chloride-catalyzed reactions prompted us to explore alternative catalysts. We hypothesized that the formation of $AlCl_3$ hydrate inhibited the reaction. Indeed, commercially available aluminum(III) chloride hexahydrate was completely inactive under the reaction conditions (Table 1, entry 13). To our delight, boron trichloride was found to produce similar yields with better consistency (Table 1, entry 14).

The scope of the reaction has been explored using phenylacetylenetrifluoroborate salt **S1** and a variety of acyl chlorides (Figure 1). Unsubstituted naphthyl and biphenyl acyl chlorides afforded the expected products in synthetically useful yields (**1b**,**c**). Benzoyl chloride derivatives bearing electron-donating substituents furnished the corresponding ynones in excellent yields (**1d**−**g**). In contrast, electron-withdrawing substituents resulted in comparatively modest yields (**1h**,**i**,**m**). The reaction was not sensitive to steric effects. High yields were observed for both para- and ortho-substituted benzoyl chloride derivatives (**1f**,**g**). Moreover, the reaction of *o*-chlorobenzoyl chloride resulted in 59% yield, which is a significant yield increase when compared to *p*-chlorobenzoyl chloride (**1h**,**i**). We hypothesize that the steric interaction of the substituent in the *ortho* position forces the carbonyl functional group out of the plane, offsetting the electron-withdrawing character of the aromatic ring. The expected ynones were obtained in good yields for both cyclohexyl and cyclopropyl carbonyl chlorides as well as acetyl chloride (**1j**−**l**). Notably, 4-bromobutyryl chloride reacted under the developed reaction conditions to afford the desired product **1m** in 39% yield. To our knowledge, this is the first protocol for the synthesis of ynones to tolerate an alkyl bromide functional group.

We further evaluated the scope of the reaction by preparing several other examples of potassium alkynyltrifluoroborate salts to examine their reactivity under the developed conditions (Figure 2). In general, derivatives of the phenylacetylenetrifluoroborate salt bearing electron-donating substituents on the aromatic ring reacted with both aromatic and aliphatic acyl chlorides to produce ynones in good to excellent yields (**2a**−**c**, **3a**−**c**). Aliphatic derivatives of the alkynyltrifluoroborate salts proved to be less reactive substrates. Modest yields were obtained when hexynyl- and cyclopentylethynyltrifluoroborate salts were reacted with electron-rich benzoyl chloride derivatives (**4a**, **5a**).

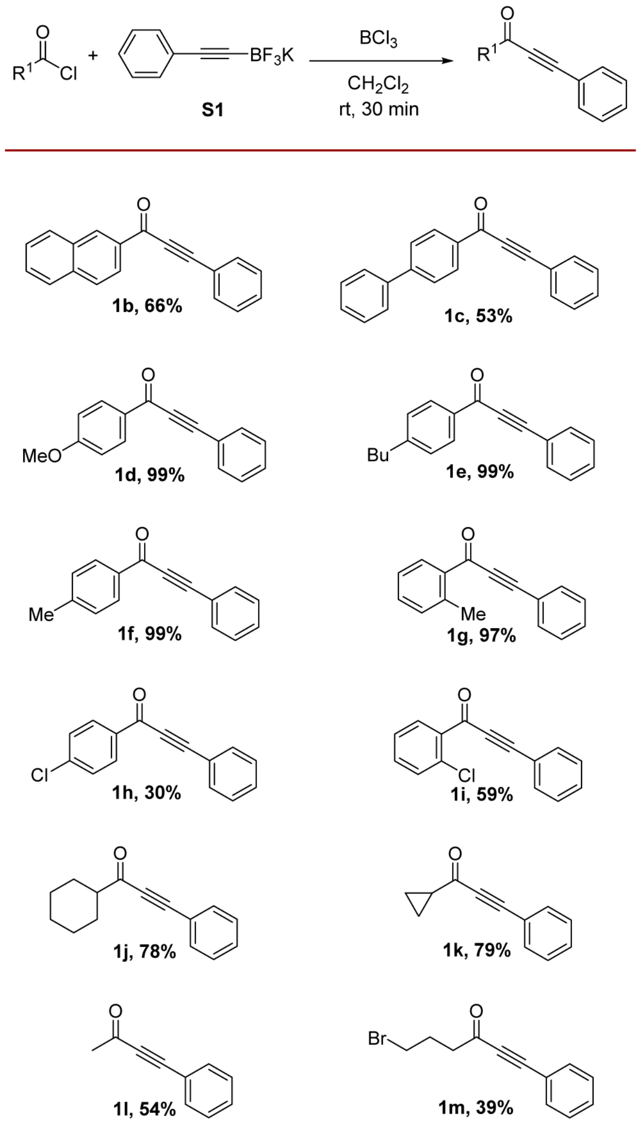


Figure 1. Reactions of phenylacetylenetrifluoroborate salt **S1** with acyl chlorides. Reactions were run with 1 equiv of acyl chloride, 1.5 equiv of potassium phenylacetylenetrifluoroborate **S1**, and 1.5 equiv of boron trichloride.

On the basis of these experiments, three plausible mechanistic pathways are proposed (Scheme 1). Upon interaction of the potassium alkynyltrifluoroborate with BCl_3, an organodichloroborane species is formed.[20] Coordination of the electrophilic organodichloroborane with the acyl chloride leads to the formation of a nucleophilic borate and an activated carbonyl functional group. Subsequent transfer of an alkynyl moiety leads to the formation of a tetrahedral intermediate, which collapses to form the desired product (path A).[21] Alternatively, coordination of the organodichloroborane species could be followed by an intramolecular chloride transfer. The generated oxocarbenium ion may combine with the organoborate to afford the desired ynone (path B). Finally, the organodichloroborane intermediate may act as a Lewis acid and react directly with the acyl chloride in a mechanism analogous

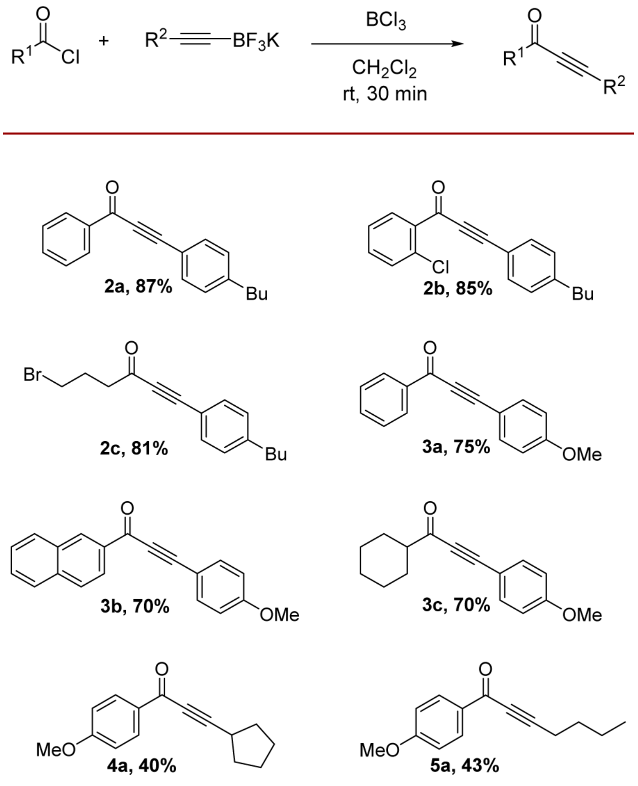
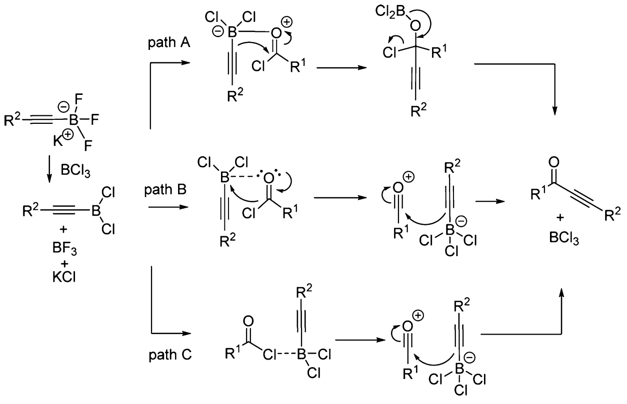


Figure 2. Reactions of various alkynyltrifluoroborates with acyl chlorides. Reactions were run with 1 equiv of acyl chloride, 2.5 equiv of potassium organotrifluoroborate salt, and 2.5 equiv of boron trichloride.

Scheme 1. Proposed Mechanistic Pathways for the Synthesis of Ynones



to that of the Friedel−Crafts reaction (path C). The electrophilic oxocarbenium intermediate may subsequently react with nucleophilic organoborate salt to form the desired product.[17c,e]

In conclusion, we have developed a novel method for the preparation of ynones from acyl chlorides and alkynyltrifluoroborate salts. This one-pot reaction proceeds rapidly in the presence of boron trichloride without exclusion of air and moisture. The value of this approach lies in functional group tolerance and the operational simplicity of the method. Under the developed reaction conditions, ynones were obtained in modest to excellent yields from a variety of acyl chlorides and alkynyltrifluoroborate salts in the presence of a Lewis acid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for organotrifluoroborate salts and compounds **1a−m**, **2a−c**, **3a−c**, **4a**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Xu, B. H.; Kehr, G.; Fröhlich, R.; Wibbeling, B.; Schirmer, B.; Grimme, S.; Erker, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 7183−7186. (b) D'Souza, D. M.; Müller, T. J. *Nat. Protoc.* **2008**, *3*, 1661−1665. (c) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4708−4711. (d) Forsyth, C. J.; Xu, J.; Nguyen, S. T.; Samdal, I. A.; Briggs, L. R.; Rundberget, T.; Sandvik, M.; Miles, C. O. *J. Am. Chem. Soc.* **2006**, *128*, 15114−15116. (e) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705−3717.

(2) (a) Bannwarth, P.; Valleix, A.; Grée, D.; Grée, R. *J. Org. Chem.* **2009**, *74*, 4646−4649. (b) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6951−6956.

(3) Arcadi, A.; Aschi, M.; Marinelli, F.; Verdecchia, M. *Tetrahedron* **2008**, *64*, 5354−5361.

(4) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 8705−8710.

(5) (a) Kirkham, J. D.; Edeson, S. J.; Stokes, S.; Harrity, J. P. *Org. Lett.* **2012**, *14*, 5354−5357. (b) Mohamed Ahmed, M. S.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487−4489.

(6) Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11*, 3210−3213.

(7) She, Z.; Niu, D.; Chen, L.; Gunawan, M. A.; Shanja, X.; Hersh, W. H.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 3627−3633.

(8) For selected references, see: (a) Matsumura, K.; Hashiguchi, S.; Ikarya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (b) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867−869. (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156.

(9) For selected references, see: (a) Logue, M. W.; Moore, G. L. *J. Org. Chem.* **1975**, *40*, 131−132. (b) Normant, J. F. *Synthesis* **1972**, 63−80.

(10) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549−2553.

(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(12) (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886. (b) Baba, T.; Kizuka, H.; Handa, H.; Ono, Y. *Appl. Catal., A* **2000**, *194*−*195*, 203−211. (c) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755. (d) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952−2953.

(13) (a) Kim, W.; Park, K.; Park, A.; Choe, J.; Lee, S. *Org. Lett.* **2013**, *15*, 1654−1657. (b) Mohamed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, *5*, 3057−3060. (c) Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1981**, 333−334.

(14) (a) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288−255. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623−3658. (c) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49−56. (d) Darses, S.; Genêt, J. P. *Eur. J. Org. Chem.* **2003**, 4313−4327.

(15) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286.

(16) Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153−2155.

(17) (a) Dumas, A. M.; Bode, J. W. *Org. Lett.* **2012**, *14*, 2138−2141. (b) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 5683−5686. (c) Vo, C.-V.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082−14089. (d) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42−45. (e) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057−18059.

(18) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P.-S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364−7369.

(19) (a) Groves, J. K. *Chem. Soc. Rev.* **1972**, *1*, 73−97. (b) Gore, P. *Chem. Rev.* **1955**, *55*, 229−281. (c) Calloway, N. *Chem. Rev.* **1935**, *17*, 327−392.

(20) Kim, B. J.; Matteson, D. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3056−3058.

(21) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151−3152.