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One-pot Synthesis of Propynoates and Propynenitriles

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An efficient transformation towards propynoates and propynenitriles was herein described. The practical methodology was conducted at low temperature (-78 or -60 °C) in a one-pot manner with assistance of base rather than any transition metal catalysts. The base-induced protocol exhibits good functional groups tolerance (up to 28 examples) and high efficiency (up to 92% yields) towards substituted acetylenes of great synthetic significance, which was also well-demonstrated by the gram-scale reactions.

Keywords: Propynoates, Propynenitriles, One-pot Preparation, Base-induced, Elimination

Introduction

Propynoates and propynenitriles^[1] have attracted widespread attention for their distinguished photoconductive or biological properties,^[2] as well their roles as the pivotal intermediates for the construction of cyclic compounds in the synthetic and pharmaceutical chemistry.^[3] Therefore, great efforts have been devoted for the synthesis of these compounds. Usually, coupling reactions mediated by transition metal catalysts such as Cu, Pd and Fe were generally utilized for the synthesis of the versatile molecules. Some unsaturated compounds like acetylenes,^[4] acetylenic bromides,^[5] arylpropionic acids,^[6] 1,1-dihalo-1-alkenes^[7] and others.^[8] were usually employed for the coupling with suitable partners. However, homo-coupling of the alkynyl substrates was unavoidable in the metallic catalysis. Thus, attempts have been devoted to seek the possibility of efficiently forming propynoates and propynenitriles without the involvement of any transition metal catalysts. Research work has been widely carried out for the construction of triple bonds from the substrates of different structure. Pioneered by Negishi^[9] and Otera,^[10] the topic has gained tremendous development thus far. For example, Tajima *et al.* reported a practical preparation of propynoates in the presence of KF.^[11] While synthesis of propynenitriles was also realized with assistance of pyridinium salts from the substrates of similar structure.^[12] As a long-standing interest of our group is aimed at the synthesis of heteroatom-substituted alkynes (S, Se, N or P),^[13] we plan to extend the general and practical methodology for the preparation of propynoates and propynenitriles with electron-deficient carbon-carbon triple bonds herein from easily-prepared starting materials.

Results and Discussion

To obtain the optimal conditions, reactions with methyl 3-phenyl-3-oxopropanoate (**1a**) as the model substrate were conducted as summarized in Table 1.

Table 1 Optimization of reaction conditions^[a]

Entry	Base	Solvent	Yield (%) ^[b]
1	<i>n</i> -BuLi	THF	n.d. ^[c]
2	LDA	THF	25
3	LiHMDS	THF	84
4	KHMDS	THF	79
5	LiHMDS	Et ₂ O	65
6 ^[d]	LiHMDS (<i>t</i> -BuOK)	THF	68
7 ^[d]	<i>t</i> -BuOK	THF	trace

^aReaction conditions: i) **1a** (0.30 mmol), base (0.33 mmol) in dry THF (3.0 mL); ii) CIP(O)(OEt)₂ (0.36 mmol) at -78 °C, then at r.t. for 30 min; iii) base (0.45 mmol) at -78 °C. ^bIsolated yields. ^cn.d. stands for not detected. ^dConditions: 1) **1a** (0.30 mmol), LiHMDS (0.33 mmol) or *t*-BuOK (0.33 mmol) in dry THF (3.0 mL); 2) CIP(O)(OEt)₂ (0.36 mmol) at -78 °C, then at r.t. for 30 min; 3) *t*-BuOK (0.45 mmol) at r.t.

As the results showed, the suitable base for the one-pot preparation was LiHMDS (entry 3), which afforded the desired product methyl 3-phenylpropynoate (**2a**) in 84% yield, and was superior to other bases such as *n*-BuLi (entry 1) and lithium diisopropyl amide (LDA, entry 2). It was noteworthy that KHMDS was also able to provide the desired product but in slightly lower yield, 79% for entry 4. THF performed better than Et₂O for the transformation, since only 65% yield of **2a** was obtained

when reaction was conducted in Et₂O (entry 5). Utilization of *t*-BuOK, either for deprotonation step or for elimination step, led to the formation of **2a** smoothly, but in lower yields (entries 6 and 7).

Now with the optimal conditions established, the scope and limitations of the substrates for the reaction were evaluated as summarized in Table 2. Except for methyl 3-phenyl-3-oxopropionate (**1a**), substrates containing electron-rich phenyl groups underwent the elimination transformation successfully towards the desired alkynyl products. For example, methyl 3-(4-methylphenyl)-3-oxopropionate (**1b**), methyl 3-(2-methylphenyl)-3-oxopropionate (**1c**), methyl 3-(4-methoxyphenyl)-3-oxopropionate (**1d**), methyl 3-(2,5-dimethoxyphenyl)-3-oxopropionate (**1e**) and methyl 3-(1,3-benzodioxol-5-yl)-3-oxopropionate (**1f**) afforded the corresponding methyl propynoates **2b** – **2f** successfully, in up to 92% yields (entries 1 – 5). Meanwhile, substrates bearing halogenated phenyl groups were well compatible with the basic conditions to produce methyl propynoates, but exhibiting general lower efficiency by comparison with the substrates with electron-rich aryl groups. For example, methyl 3-(4-fluorophenyl)-2-propynoate (**2g**), methyl 3-(4-chlorophenyl)-2-propynoate (**2h**), methyl 3-(4-bromophenyl)-2-propynoate (**2i**) and even methyl 3-(4-iodophenyl)-2-propynoate (**2j**) were afforded smoothly under the optimal conditions, in yields ranging from 78% to 83% (entries 6 – 9). Di-halogenated substrate **1k** led to the methyl 3-(3,4-dichlorophenyl)-2-propynoate (**2k**) in slightly lower yield, 80% for entry 10. Moreover, biaryl substituted substrates was also able to afford the desired products readily. For instance, methyl 3-(4,4'-biphenyl)-2-propynoate (**2l**), methyl 3-(naphthalene-2-yl)-2-propynoate (**2m**) and methyl 3-(6-methoxynaphthalene-2-yl)-2-propynoate (**2n**) were furnished in yields from 78% to 81% (entries 11 – 13). It was noteworthy that the hetero-aromatic groups were also well-tolerated in the transformation under the optimal conditions, for methyl 3-(2-furanyl)-2-propynoate (**2o**) and methyl 3-(2-thiophenyl)-2-propynoate (**2p**) were obtained in 75% and 78% yields, respectively (entries 14 and 15). Also, ethyl 3-phenyl-2-propynoate **2q** was produced under the optimal conditions in 88% yield (entry 16).

Table 2 Substrate scope for the synthesis of propynoates^[a]

$ \begin{array}{c} \text{O} \\ \parallel \\ (\text{Het})\text{Ar}-\text{C}-\text{COOR} \\ \text{1} \end{array} \xrightarrow[\text{iii) LiHMDS, -78 }^\circ\text{C}]{\text{i) LiHMDS, THF, -78 }^\circ\text{C}; \text{ii) CIP(O)(OEt)}_2, -78 }^\circ\text{C} - \text{r.t.}} \begin{array}{c} (\text{Het})\text{Ar}-\text{C}\equiv\text{C}-\text{COOR} \\ \text{2} \end{array} $			
Entry	2	(Het)Ar, R	Yield (%) ^b
1	2b	4-CH ₃ C ₆ H ₄ , CH ₃	84
2	2c	2-CH ₃ C ₆ H ₄ , CH ₃	92

3	2d	4-CH ₃ OC ₆ H ₄ , CH ₃	91
4	2e	2,5-(CH ₃ O) ₂ C ₆ H ₃ , CH ₃	92
5	2f	-COOMe	84
6	2g	4-FC ₆ H ₄ , CH ₃	82
7	2h	4-ClC ₆ H ₄ , CH ₃	83
8	2i	4-BrC ₆ H ₄ , CH ₃	80
9	2j	4-IC ₆ H ₄ , CH ₃	78
10	2k	3,4-Cl ₂ C ₆ H ₃ , CH ₃	80
11	2l	4-PhC ₆ H ₄ , CH ₃	78
12	2m	2-Naphthyl, CH ₃	81
13	2n	6-CH ₃ O-2-naphthyl, CH ₃	80
14	2o	2-Furyl, CH ₃	75
15	2p	2-Thiophenyl, CH ₃	78
16	2q	Ph, CH ₂ CH ₃	88

[a] Reaction conditions: i) **1** (0.50 mmol), LiHMDS (1.0 M in THF, 0.55 mmol), dry THF (5.0 mL) at -78 °C for 30 min; ii) CIP(O)(OEt)₂ (0.60 mmol) at -78 °C and then at r.t. for 30 min; iii) LiHMDS (1.0 M in THF, 0.75 mmol) at -78 °C for 1 h. [b] Isolated yields.

Encouraged by the broad substrate scope of the one-pot preparation towards propiolic acid esters, the applicability of the alkynylation method in the synthesis of 2-propynenitriles in the same manner was further explored as shown in Table 3. Pleasingly, under the similar conditions but at a relatively higher temperature (-60 °C), 3-phenyl-2-propynenitriles (**4a**) was obtained in the one-pot preparation protocol from 3-oxo-3-phenylpropionitrile (**3a**) in an excellent yield, up to 85% (entry 1). Analogously, electron-rich phenyl groups were firstly evaluated in the transformation. Both mono- and disubstituted phenyl groups were well-tolerated in the system. As shown, 3-oxo-3-(4-methylphenyl) propionitrile (**3b**), 3-oxo-3-(3-methylphenyl) propionitrile (**3c**), 3-oxo-3-(2-methylphenyl) propionitrile (**3d**) and 3-oxo-3-(3,4-dimethoxyphenyl) propionitrile (**3e**) successfully afforded the corresponding electron-rich phenyl groups decorated 2-propynenitriles **4b** – **4e** in yields from 82% to 91% (entries 2 – 5). Meanwhile, it is noteworthy that the properties of the substituents on the phenyl groups of the substrates did not affect the yields significantly. And it was observed that halogenated phenyl groups also exhibited good compatibility in the transformation. *Para*- or *ortho*- halogenated phenyl groups showed slight influence on the yields of the desired products. For example, 3-oxo-3-(4-chlorophenyl) propionitrile (**3f**) and 3-oxo-3-(4-bromophenyl) propionitrile (**3h**) furnished the desired products in 86% and 85% yields, while 3-(2-chlorophenyl)-2-propynenitriles (**4g**) and 3-(2-bromophenyl)-2-propynenitriles (**4i**) were obtained in 90% yield (entries 6 – 9). In the same man-

ner, polyaryl decorated substrates such as 3-oxo-3-(4,4'-biphenyl) propionitrile (**3j**) and 3-oxo-3-(naphthalene-2-yl) propionitrile (**3k**) offered biphenyl or 2-naphthyl fused 2-propynenitriles **4j** and **4k** in 89% and 83% yields, respectively (entries 10 and 11).

Table 3 Substrate scope for the synthesis of 2-propynenitriles^[a]

Entry	4	Ar	Yield (%) ^b
1	4a	Ph	85
2	4b	4-CH ₃ C ₆ H ₄	82
3	4c	3-CH ₃ C ₆ H ₄	85
4	4d	2-CH ₃ C ₆ H ₄	83
5	4e	3,4-(CH ₃ O) ₂ C ₆ H ₃	91
6	4f	4-ClC ₆ H ₄	86
7	4g	2-ClC ₆ H ₄	90
8	4h	4-BrC ₆ H ₄	85
9	4i	2-BrC ₆ H ₄	90
10	4j	4-PhC ₆ H ₄	89
11	4k	2-Naphthyl	83

[a] Conditions: i) **3** (0.50 mmol), LiHMDS (1.0 M in THF, 0.55 mmol), dry THF (5.0 mL) at -60 °C for 30 min; ii) ClP(O)(OEt)₂ (0.6 mmol) at -60 °C and then at r.t. for 30 min; iii) LiHMDS (1.0 M in THF, 0.75 mmol) at -60 °C 1 h. [b] Isolated yields.

Based on previously demonstrated mechanistic study by our group,^[13] a plausible mechanism for the present one-pot preparation of propynoates and propynenitriles was proposed. As illustrated in Scheme 1, treatment of the substrates with a strong base LiHMDS (1.1 equivalents) led to an intermediate **A**, which allowed an easy in situ generation of another intermediate **B** in the enolate form. Then, a nucleophilic attack of the intermediate **B** to ClP(O)(OEt)₂ formed enol phosphate intermediate **C**, which underwent an elimination step upon the treatment of an additional 1.5 equivalents of LiHMDS, affording the corresponding products propynoates or propynenitriles. However, efforts to isolate of the key intermediate **C** with flash column chromatography (SiO₂) failed, probably because that C=C bonds decomposed during the workup procedure.

Scheme 1. Proposed mechanism

Furthermore, to demonstrate the scalability of the one-pot alkylation method for preparing propynoates and propynenitriles, gram-scale experiments were carried out as shown in Scheme 2. Under the optimized conditions and in the same concentration (0.1 M), 10 mmol of the substrates **1a** or **3a** furnished 1.25 g **2a** and 0.96 g **4a**, in 78% and 76% yields, respectively, reasonably lower than the yields of small-scale reactions (0.30 to 0.50 mmol). And the good results showed the promise of the synthetic method for larger-scale synthesis of some rare alkynyl derivatives.

Scheme 2. Gram-scale experiments

Conclusions

In summary, we have disclosed a practical synthetic method towards propynoates and propynenitriles in a one-pot manner. The products of great importance were obtained in good to excellent yields with broad substrate scope and high efficiency, which was illustrated well by the scaled-up experiments.

Materials and method

Solvents, reagents were purchased as analytical grade chemicals and used without further purification. Column chromatography was performed on silica gel (200-300 mesh). ¹H and ¹³C NMR spectra were recorded on a Varian INOVA-400 spectrometer in deuterated chloroform at 25 °C with residual solvent peaks as internal standards (δ = 7.26 ppm for ¹H-NMR and δ = 77.16 ppm for ¹³C-NMR). Chemical shifts (δ) are reported in ppm, and spin-spin coupling constants (*J*) are given in Hz, while multiplicities are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded on a ThermoFinni-

gan MAT95XP microspectrometer and high resolution mass spectra (HRMS) were recorded on an Agilent Technologies Accurate Mass Q-TOF 6530 microspectrometer. Melting points were recorded on a national standard melting point apparatus (Model: Taikex XT-4) and were uncorrected.

Experimental

Under the nitrogen atmosphere, LiHMDS (0.55 mL, 1.0 mol/L in THF/ethylbenzene) was added dropwise to the solution of substrate **1** or **3** (0.50 mmol) in dry THF (5.0 mL) at referred temperature and the mixture was kept stirred for additional 30 min. Then ClP(O)(OEt)₂ (0.60 mmol) was added to the above solution. After addition, the mixture was warmed up to the room temperature gradually and kept stirred for another 30 min. The mixture was then re-cooled to the referred temperature, LiHMDS (0.75 mL, 1.0 mol/L in THF/ethylbenzene) was added dropwise to the solution. The mixture was kept stirred at the maintained temperature for another 1 h, then, quenched with saturated NH₄Cl (aq.). The water phase extracted with EtOAc (20 mL × 3). The combined organic phase was dried over anhydrous Na₂SO₄; solvent was removed by rotary evaporation and the resulting oily mixture was purified with silica gel flash column chromatograph (elute: hexanes), giving the desired products **2** or **4** in noted yields.

Data

Methyl 3-phenyl-2-propynoate (**2a**)

Colorless oil. Yield: 85% (68 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.58 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 3.84 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 154.6, 133.1, 130.8, 128.7, 119.7, 86.7, 80.5, 52.9. MS (EI) *m/z* (%): 75.1 (14), 102.1 (26), 129.1 (100), 118.1 (100), 160.1 (M⁺, 29). HRMS (EI): calcd. for [C₁₀H₈O₂]⁺: 160.0524, Found 160.0519.

Methyl 3-(4-methylphenyl)-2-propynoate (**2b**)

Colorless crystal, m.p.: 63 - 65 °C. Yield: 84% (73 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.48 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 154.8, 141.5, 133.2, 129.5, 116.5, 87.2, 80.2, 52.9, 21.9. MS (EI) *m/z* (%): 115.1 (14), 116.1 (38), 143.1 (100), 174.1 (M⁺, 47). HRMS (EI): calcd. for [C₁₁H₁₀O₂]⁺: 174.0681, Found 174.0675.

Methyl 3-(2-methylphenyl)-2-propynoate (**2c**)

Colorless oil. Yield: 92% (80 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.53 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.5

Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 2.48 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 154.69, 142.3, 133.5, 130.8, 129.9, 125.9, 119.4, 85.6, 84.3, 52.8, 20.6. MS (EI) *m/z* (%): 91.1 (18), 115.1(100), 116.1 (52), 129.1 (12), 143.1 (74), 174.1 (M⁺, 47). HRMS (EI): calcd. for [C₁₁H₁₀O₂]⁺: 174.0681, Found 174.0675.

Methyl 3-(4-methoxyphenyl)-2-propynoate (**2d**)

Colorless crystal, m.p.: 34 - 36 °C. Yield: 91% (87 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.53 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 3.82(s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 161.7, 154.9, 135.1, 114.4, 111.43, 87.5, 79.95, 55.5, 52.8. MS (EI) *m/z* (%):116.1 (14), 132.1 (74), 144.1 (19), 159.1 (100), 190.1 (M⁺, 56). HRMS (EI): calcd. for [C₁₁H₁₀O₃]⁺: 190.0630, Found 190.0624.

Methyl 3-(2,5-dimethoxyphenyl)-2-propynoate (**2e**)

Colorless crystal, m.p.: 69 - 71 °C. Yield: 92% (101 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.03 (d, *J* = 3.1 Hz, 1H), 6.95 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 156.3, 154.6, 153.1, 119.0, 118.8, 112.3, 109.0, 84.1, 83.6, 56.43, 55.9, 52.8. MS (EI) *m/z* (%):77.1 (23), 131.1 (36), 89.1 (30), 147.1 (39), 189.1 (17), 205.1(44),220.1 (M⁺, 100). HRMS (EI): calcd. for [C₁₂H₁₂O₄]⁺: 220.0736, Found 220.0731.

Methyl 3-(1,3-benzodioxol-5-yl)-2-propynoate (**2f**)

Colorless crystal, m.p.: 71 - 73 °C. Yield: 84% (86 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.15 (d, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H), 3.82 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 154.7, 150.2, 147.8, 129.0, 112.7, 112.6, 108.9, 101.9, 87.1, 79.5, 52.8; MS (EI) *m/z* (%):63.1 (28), 83.0(21),119.1 (34), 171.1 (48), 202.1(M⁺, 100); HRMS (EI): calcd. for [C₁₁H₈O₄]⁺: 204.0423, found 204.0427.

Methyl 3-(4-fluorophenyl)-2-propynoate (**2g**)

Colorless crystal, m.p.: 52 - 54 °C. Yield: 82% (73 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.51 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.00 (dd, *J* = 8.6, 5.4 Hz, 2H), 3.77 (s, 3H). ¹³C-NMR (100 MHz, CDCl₃) (ppm): 164.1 (*J*_{C-F} = 252 Hz), 154.5, 135.4 (*J*_{C-F} = 9.0 Hz), 116.3 (*J*_{C-F} = 22.0 Hz), 85.6, 80.4, 52.96; MS (EI) *m/z* (%):74.1 (5), 99.1 (19), 120.1 (39), 147.1 (100), 178.1 (M⁺, 27). HRMS (EI): calcd. for [C₁₀H₇O₂F]⁺: 178.0430, found 178.0428.

Methyl 3-(4-chlorophenyl)-2-propynoate (**2h**)

Off-white solid, m.p.: 87-89 °C. Yield: 83% (81 mg). ¹H-NMR (400 MHz, CDCl₃) (ppm): 7.51 (d, *J* = 8.4 Hz,

2H), 7.36 (d, $J = 8.4$ Hz, 2H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.4, 137.3, 134.3, 129.2, 118.1, 85.3, 81.3, 53.0; MS (EI) m/z (%): 74.1 (12), 99.1 (24), 136.0 (46), 163.0 (100), 194.0 (M^+ , 29). HRMS (EI): calcd. for $[\text{C}_{10}\text{H}_7\text{O}_2\text{Cl}]^+$: 194.0135, found 194.0134.

Methyl 3-(4-bromophenyl)-2-propynoate (**2i**)

Off-white solid, m.p.: 97–99 °C. Yield: 80% (95 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.52 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.4, 134.4, 132.2, 125.7, 118.6, 85.4, 81.4, 53.0; MS (EI) m/z (%): 100.1 (27), 128.1 (49), 180.0 (100), 182.0 (96), 207.0 (24), 238.0 (M^+ , 23). HRMS (EI): calcd. for $[\text{C}_{10}\text{H}_7\text{O}_2\text{Br}]^+$: 237.9629, found 237.9629.

Methyl 3-(4-iodophenyl)-2-propynoate (**2j**)

Off-white solid, m.p.: 100–102 °C. Yield: 78% (112 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.52 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.4, 134.4, 132.2, 125.7, 118.6, 85.4, 81.4, 53.0; MS (EI) m/z (%): 74.1 (15), 99.1 (26), 121.1 (48), 203.0 (90), 227.0 (100), 286.0 (M^+ , 30); HRMS (EI): calcd. for $[\text{C}_{10}\text{H}_7\text{O}_2\text{I}]^+$: 285.9491, found 285.9485.

Methyl 3-(3,4-dichlorophenyl)-2-propynoate (**2k**)

Light yellow solid, m.p.: 68–70 °C. Yield: 80% (91 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.66 (d, $J = 1.4$ Hz, 1H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.40 (dd, $J = 8.3, 1.4$ Hz, 1H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.1, 135.7, 134.6, 133.3, 132.0, 130.9, 119.6, 83.6, 81.9, 53.1; MS (EI) m/z (%): 74.1 (10), 98.2 (25), 133.1 (14), 170.1 (50), 197.0 (100), 229.1 (M^+ , 2). HRMS (EI): calcd. for $[\text{C}_{10}\text{H}_6\text{O}_2\text{Cl}_2]^+$: 227.9745, found 227.9749.

Methyl 3-(4,4'-biphenyl)-2-propynoate (**2l**)

Off-white solid, m.p.: 70–72 °C. Yield: 78% (92 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.66 (d, $J = 8.3$ Hz, 2H), 7.60 (dd, $J = 7.7, 5.8$ Hz, 4H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.39 (t, $J = 7.2$ Hz, 1H), 3.86 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.6, 143.6, 139.9, 133.6, 129.1, 128.3, 127.4, 127.2, 118.3, 86.7, 81.1, 52.9; MS (EI) m/z (%): 176.1 (44), 178.1 (95), 205.1 (100), 236.1 (M^+ , 81). HRMS (EI): calcd. for $[\text{C}_{16}\text{H}_{12}\text{O}_2]^+$: 236.0837, found 236.0836.

Methyl 3-(naphthalene-2-yl)-2-propynoate (**2m**)

Off-white solid, m.p.: 123 – 124 °C. Yield: 81% (85 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 8.15 (s, 1H), 7.86 – 7.79 (m, 3H), 7.54 (ddd, $J = 10.3, 9.6, 7.2$ Hz, 3H), 3.87 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.6,

134.4, 134.0, 132.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.1, 116.8, 87.1, 80.7, 53.0; MS (EI) m/z (%): 150.1 (28), 152.1 (69), 179.1 (94), 210.1 (M^+ , 100). HRMS (EI): calcd. for $[\text{C}_{14}\text{H}_{10}\text{O}_2]^+$: 210.0681, found 210.0674.

Methyl 3-(6-methoxynaphthalene-2-yl)-2-propynoate (**2n**)

Off-white solid, m.p.: 103–105 °C. Yield: 80% (96 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 8.06 (s, 1H), 7.70 (t, $J = 8.0$ Hz, 2H), 7.53 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.18 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.11 (d, $J = 2.0$ Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 159.4, 154.8, 135.6, 134.3, 129.9, 129.1, 128.2, 127.3, 120.1, 114.2, 106.0, 87.7, 80.3, 55.5, 52.9; MS (EI) m/z (%): 139.1 (27), 165.1 (28), 182.1 (72), 209.1 (61), 240.1 (M^+ , 100). HRMS (EI): calcd. for $[\text{C}_{15}\text{H}_{12}\text{O}_3]^+$: 240.0786, found 240.0780.

Methyl 3-(2-furanyl)-2-propynoate (**2o**)

Light yellow liquid. Yield: 75% (56 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.51 (s, 1H), 6.94 (d, $J = 3.4$ Hz, 1H), 6.47 (dd, $J = 3.3, 1.8$ Hz, 1H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.2, 146.4, 134.7, 121.3, 111.7, 85.7, 76.9, 53.0; MS (EI) m/z (%): 63.1 (20), 92.1 (76), 109.1 (4), 119.1 (100), 150.1 (M^+ , 40). HRMS (EI): calcd. for $[\text{C}_8\text{H}_6\text{O}_3]^+$: 150.0317, found 150.0313.

Methyl 3-(2-thiophenyl)-2-propynoate (**2p**)

Light yellow liquid, Yield: 78% (65 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.48 (dd, $J = 8.9, 4.4$ Hz, 2H), 7.05 (dd, $J = 4.8, 4.0$ Hz, 1H), 3.84 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.5, 136.7, 131.3, 127.7, 119.5, 84.7, 80.7, 52.9; MS (EI) m/z (%): 63.1 (14), 89.1 (45), 107.1 (41), 135.1 (100), 166.0 (M^+ , 53). HRMS (EI): calcd. for $[\text{C}_8\text{H}_6\text{O}_2\text{S}]^+$: 166.0089, found 166.0086.

Ethyl 3-phenyl-2-propynoate (**2q**)

Colorless oil, Yield: 88% (77 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.58 (d, $J = 7.3$ Hz, 2H), 7.44 (t, $J = 7.4$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 154.2, 133.1, 130.7, 128.7, 119.8, 86.2, 80.8, 62.2, 14.2; MS (EI) m/z (%): 75.1 (13), 102.1 (64), 129.1 (100), 130.1 (17), 174.1 (M^+ , 18). HRMS (EI): calcd. for $[\text{C}_{11}\text{H}_{10}\text{O}_2]^+$: 174.0681, found 174.0676.

3-Phenyl-2-propynenitriles (**4a**)

Colorless oil, Yield: 85% (54 mg). ^1H -NMR (400 MHz, CDCl_3) (ppm): 7.61 (d, $J = 8.1$ Hz, 2H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 2H). ^{13}C -NMR (100 MHz, CDCl_3) (ppm): 133.7, 132.0, 129.0, 117.7, 105.6, 83.1,

63.3; MS (EI) m/z (%): 77 (6), 89 (3), 140 (13), 164 (10), 224 (2), 281 (59), 293 (17), 309 (36), 324 (M^+ , 100); HRMS (EI): calcd. for $[C_9H_5N]^+$: 127.0422, found 127.0420.

3-(4-Methylphenyl)-2-Propynenitrile (**4b**)

Colorless oil, Yield: 82% (58 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.50 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 142.9, 133.6, 129.8, 114.6, 105.8, 83.6, 62.9, 22.0; MS (EI) m/z (%): 63.1 (10), 113.1 (16), 114.1 (40), 140.1 (100), 141.1 (M^+ , 87). HRMS (EI): calcd. for $[C_{10}H_7N]^+$: 141.0578, found 141.0573.

3-(3-Methylphenyl)-2-Propynenitrile (**4c**)

Colorless oil, Yield: 85% (60 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.40 (d, J = 6.6 Hz, 2H), 7.35 – 7.24 (m, 2H), 2.35 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 139.0, 134.0, 132.9, 130.8, 128.9, 117.5, 105.7, 83.5, 62.9, 21.3; MS (EI) m/z (%): 113.1 (14), 114.1 (35), 140.1 (100), 141.1 (M^+ , 90). HRMS (EI): calcd. for $[C_{10}H_7N]^+$: 141.0578, found 141.0572.

3-(2-Methylphenyl)-2-Propynenitrile (**4d**)

Colorless oil. Yield: 83% (59 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.58 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 2.50 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 143.5, 134.2, 131.9, 130.2, 126.2, 117.5, 105.7, 82.5, 66.5, 20.6; MS (EI) m/z (%): 57.2 (6), 63.1 (24), 114.1 (38), 139.1 (9), 140.1 (100), 141.1 (M^+ , 83). HRMS (EI): calcd. for $[C_{10}H_7N]^+$: 141.0578, found 140.0598.

3-(3,4-Dimethoxyphenyl)-2-Propynenitrile (**4e**)

Yellow foamy solid, m.p.: 98–100 °C. Yield: 91% (85 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.25 (dd, J = 8.4, 1.6 Hz, 1H), 7.03 (d, J = 1.3 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 152.6, 149.0, 128.2, 115.2, 111.3, 109.2, 105.9, 83.9, 62.3, 56.1; MS (EI) m/z (%): 75.1 (11), 89.1 (17), 116.1 (20), 126.1 (9), 144.1 (20), 172.1 (28), 187.1 (M^+ , 100). HRMS (EI): calcd. for $[C_{11}H_9O_2N]^+$: 187.0633, found 187.0634.

3-(4-Chlorophenyl)-2-Propynenitrile (**4f**)

Off-white solid, m.p.: 94–96 °C. Yield: 86% (69 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.55 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 138.4, 133.0, 127.1, 118.3, 105.3, 79.4, 67.4; MS (EI) m/z (%): 51.0 (12), 75.1 (6), 99.1 (27), 126.1 (78), 161.1 (M^+ , 100). HRMS (EI): calcd. for $[C_9H_4NCl]^+$: 161.0032, found 161.0033.

3-(2-Chlorophenyl)-2-Propynenitrile (**4g**)

Colorless crystal. m.p.: 92–94 °C. Yield: 90% (72 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.63 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 3.9 Hz, 2H), 7.35 – 7.29 (m, 1H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 138.4, 135.4, 132.9, 130.1, 127.1, 118.3, 105.3, 79.4, 67.4; MS (EI) m/z (%): 51.0 (12), 99.1 (24), 100.1 (17), 126.1 (46), 161.1 (M^+ , 100). HRMS (EI): calcd. for $[C_9H_4NCl]^+$: 161.0032, found 161.0032.

3-(4-Bromophenyl)-2-Propynenitrile (**4h**)

Off-white solid. m.p.: 108–110 °C. Yield: 85% (88 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.57 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 134.8, 132.5, 127.1, 116.6, 105.4, 81.9, 64.3; MS (EI) m/z (%): 51.0 (5), 75.1 (7), 99.0 (20), 100.0 (15), 126.1 (17), 205.0 (M^+ , 100); HRMS (EI): calcd. for $[C_9H_4NBr]^+$: 204.9527, found 204.9528.

3-(2-Bromophenyl)-2-Propynenitrile (**4i**)

Off-white solid. m.p.: 58–60 °C. Yield: 90% (108 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.68 – 7.58 (m, 2H), 7.43 – 7.33 (m, 2H); ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 135.6, 133.2, 132.9, 127.6, 127.2, 120.6, 105.4, 80.9, 66.8; MS (EI) m/z (%): 51.0 (3), 99.1 (17), 126.1 (41), 203.1 (7), 205.0 (M^+ , 100). HRMS (EI): calcd. for $[C_9H_4NBr]^+$: 204.9527 found 204.9527.

3-(4,4'-Biphenyl)-2-Propynenitrile (**4j**)

Off-white solid. m.p.: 83–85 °C. Yield: 89% (90 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 7.71 – 7.57 (m, 6H), 7.49 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 144.8, 139.5, 134.1, 129.2, 128.7, 127.6, 127.3, 116.22, 105.7, 83.2, 63.8; MS (EI) m/z (%): 61.1 (8), 86.1 (35), 115.1 (9), 146.1 (74), 173.1 (100), 203.1 (M^+ , 2). HRMS (EI): calcd. for $[C_{15}H_9N]^+$: 203.0735, found 203.0738.

3-(Naphthalene-2-yl)-2-Propynenitrile (**4k**)

Yellowish solid. m.p.: 72 – 74 °C. Yield: 83% (73 mg). 1H -NMR (400 MHz, $CDCl_3$) (ppm): 8.18 (s, 1H), 7.86 (dd, J = 7.5, 5.6 Hz, 3H), 7.58 (ddd, J = 16.5, 11.4, 3.5 Hz, 3H). ^{13}C -NMR (100 MHz, $CDCl_3$) (ppm): 135.6, 134.4, 132.50, 128.9, 128.9, 128.3, 128.1, 127.9, 127.6, 114.7, 105.7, 83.7, 63.3; MS (EI) m/z (%): 75.1 (7), 99.1 (3), 150.1 (19), 175.1 (6), 177.1 (M^+ , 100). HRMS (EI): calcd. for $[C_{13}H_7N]^+$: 177.0578, found 177.0576.

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One-pot Synthesis of Propynoates and Propynenitriles

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Y = COOR or CN

An efficient transformation towards ester or nitril substituted alkynes was herein described. The practical methodology was conducted at low temperature (-78 or -60 °C) in a one-pot manner with assistance of LiHMDS. The base-induced protocol exhibits good functional groups tolerance (up to 28 examples) and high efficiency (up to 92% yields) towards substituted acetylenes of great synthetic significance, which was also well-demonstrated by the gram-scale reactions.