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EFFICIENT SYNTHESIS OF ACRYLATES BEARING AN ARYL OR HETEROARYL MOIETY: ONE-POT METHOD FROM AROMATICS AND HETEROAROMATICS USING FORMYLATION AND THE HORNER-WADSWORTH-EMMONS REACTION

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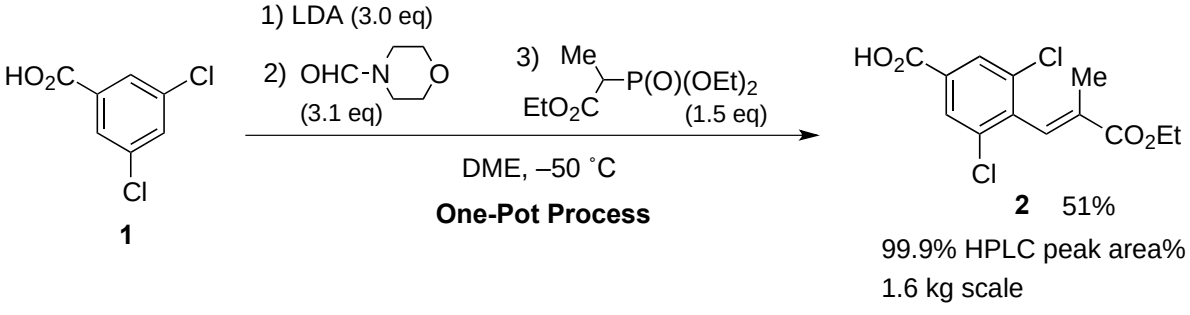
Abstract – Acrylates bearing an aryl or heteroaryl moiety were efficiently prepared by a one-pot process employing a sequence of lithiation, formylation and the Horner-Wadsworth-Emmons reaction starting from aromatic and heteroaromatic compounds. This method can efficiently introduce an acrylate moiety into aromatic and heteroaromatic compounds.

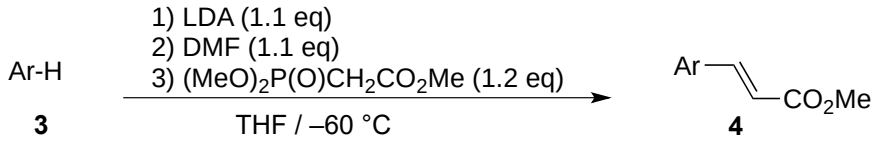
Acrylates bearing an aryl or heteroaryl moiety (cinnamic acid derivatives and their analogues) are useful chemical species for synthetic chemistry. They can be prepared by formylation of aromatics or heteroaromatics followed by the Horner-Wadsworth-Emmons reaction,[1,2] but this stepwise reaction method usually requires isolation steps entailing tedious synthetic procedures. One-pot preparation methods of these products from aromatics have been reported, but the aromatic substrates are limited to commercially available phenyllithium or phenols.[3] One example is known of a one-pot preparation method from aryl halides by lithium-halogen exchange,[2] but there has been no report of a one-pot synthesis of acrylates bearing an aryl moiety from aromatics without using lithium-halogen exchange.[4]

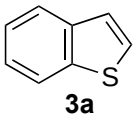
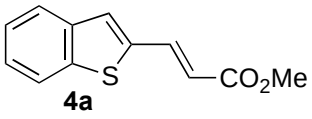
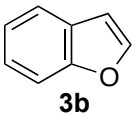
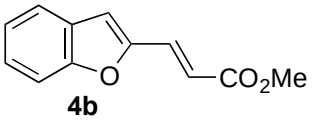
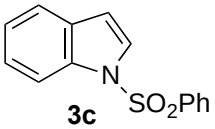
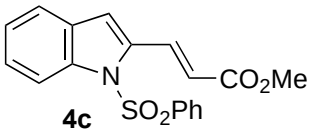
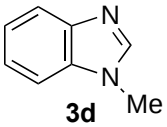
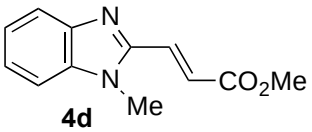
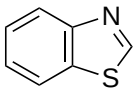
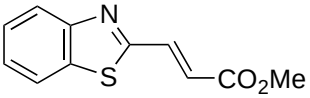
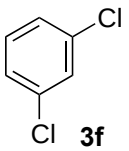
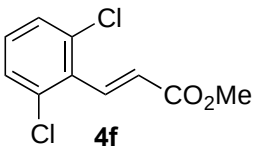
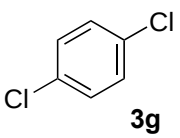
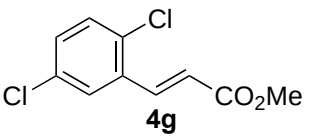


Scheme 1. One-pot preparation method for methacrylate derivative **2** from aromatic compound **1**

We have already reported a one-pot preparation process of a methacrylate derivative **2** starting from 3,5-dichlorobenzoic acid (**1**) by sequential lithiation, formylation and the Horner-Wadsworth-Emmons reaction (Scheme 1).[5] This very useful and efficient one-pot process enables kilogram-scale manufacturing of a methacrylate having an aryl moiety (**2**). Here we report a one-pot preparation method of acrylates bearing an aryl or heteroaryl moiety from various aromatic and heteroaromatic compounds.

Table 1. One-pot method for the preparation of acrylate bearing an aryl or heteroaryl moiety



entry	substrate	product	yield (%)
1	 **3a**	 **4a**	81[a]
2			87
3	 **3b**	 **4b**	83
4	 **3c**	 **4c**	72
5	 **3d**	 **4d**	89[b]
6	 **3e**	 **4e**	83
7	 **3f**	 **4f**	88[c]
8	 **3g**	 **4g**	67[c]

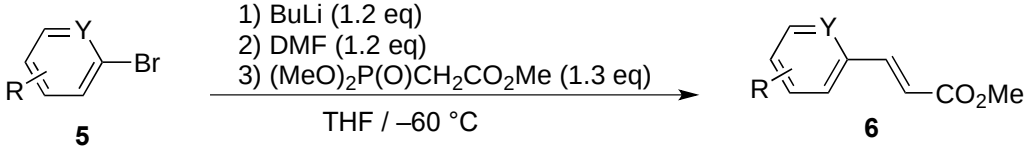
[a]: *n*-BuLi (1.1 eq) was used as a lithiating agent instead of LDA
[b]: carried out at –30 °C
[c]: carried out in 1,2-dimethoxyethane (DME)

We developed a one-pot preparation method of aryl or heteroaryl-bearing acrylates from heteroaromatic compounds. The results are summarized in Table 1. Benzothiophene (**3a**) was lithiated with BuLi or LDA (lithium diisopropylamide) and the resulting aryllithium was formylated by DMF (*N*,*N*-dimethylformamide) and subsequently subjected to olefination by the Horner-Wadsworth-Emmons reaction using trimethyl phosphonoacetate to give a desired acrylate derivative **4a** in a one-pot process with good yield (entries 1-2). Other heteroaryl-bearing acrylates were also prepared from heteroaromatics by using LDA as a lithiating agent in good to satisfactory yield (entries 3-6). The reactions proceeded smoothly and were completed within 3 h (lithiation, formylation, and the Horner-Wadsworth-Emmons reaction).

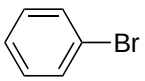
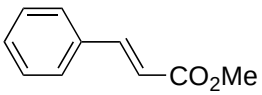
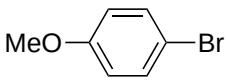
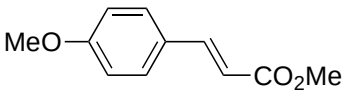
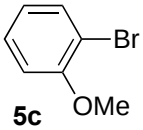
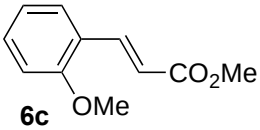
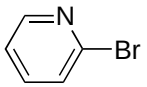
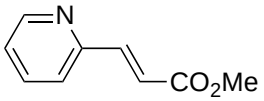
Similar to Scheme 1, 1,3-dichlorobenzene and 1,4-dichlorobenzene were converted to the corresponding cinnamic acid esters (**4f**, **4g**) in a one-pot manner (entries 7-8).

This one-pot method can also be used with the substrates of aryl bromide, which is a precursor of aryllithium (Table 2). Aryl bromides were converted to aryllithiums by lithium-halogen exchange and were successfully converted to the corresponding aryl-bearing acrylates in moderate to satisfactory yield in a one-pot manner.

Table 2. One-pot method for the preparation of aryl-bearing acrylates from aryl bromides



5 **6**

entry	substrate	product	yield (%)
1	 **5a**	 **6a**	72
2	 **5b**	 **6b**	80
3	 **5c**	 **6c**	80
4	 **5d**	 **6d**	68

The conversion from aryl bromides to aryl-bearing acrylates shown in Table 2 is possible by the Mizoroki-Heck reaction. However, the one-pot method shown in Table 2 has the advantage of not requiring any transition metal catalysts such as palladium, which can reduce manufacturing cost and avoid contamination of residual transition metal in the product.

In conclusion, we have developed a one-pot preparation method for aryl or heteroaryl-bearing acrylates from aromatic and heteroaromatic compounds. This method is useful in terms of synthetic efficiency, as the three reactions involved (lithiation, formylation, the HWE reaction) proceed successively in a one-pot manner. Our synthetic method is also beneficial for large-scale production, offering labor-saving and simple operational features.

EXPERIMENTAL

General: All materials were purchased from commercial suppliers. Unless otherwise specified, all reagents and solvents were used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker AVANCE III HD 400 spectrometer, and mass spectra on a SHIMADZU LCMS-2010EV spectrometer. High resolution mass spectra were determined with a Thermo Fisher SCIENTIFIC Q Exactive Focus and infrared spectra with a Bruker VERTEX 70. The melting points (mp) were obtained using a METTLER TOLEDO DSC822e Differential Scanning Calorimeter (DSC).

Typical experimental procedure for one-pot preparation of aryl or heteroaryl-bearing acrylates (4). Methyl (*E*)-3-(benzo[*b*]thiophen-2-yl)acrylate (4a):[6] (Table 1, entry 2)

To a solution of **3a** (161 mg, 1.20 mmol) in THF (4.0 mL) was added dropwise lithium diisopropylamide (1.93 M solution in THF/heptane/ethylbenzene, 0.68 mL, 1.3 mmol) at dry ice-acetone bath temperature with stirring for 1 h. To the solution was added dropwise DMF (0.10 mL, 1.3 mmol), and the reaction mixture was allowed to warm to ice-bath temperature and stirred for 30 min. Trimethyl phosphonoacetate (0.21 mL, 1.5 mmol) was added and stirring at ice-bath temperature was continued for 1 h. Aqueous 5% HCl (2 mL) and water (4 mL) were added successively and the mixture was extracted with EtOAc (10 mL). The organic layer was separated and washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated. The residual oil was subjected to column chromatography (silica gel) to give **4a** (229 mg, 87%) as a white solid; mp 125.3 °C; ^{1}H NMR δ 7.88 (1H, d, *J* = 16 Hz), 7.80-7.75 (2H, m), 7.46 (1H, s), 7.40-7.33 (2H, m), 6.30 (1H, d, *J* = 16 Hz), 3.82 (3H, s); ^{13}C NMR δ 166.94, 140.20, 139.54, 139.45, 137.83, 128.64, 126.22, 124.85, 124.42, 122.45, 119.06, 51.78; MS *m/z* 219 ($[M+H]^+$).

Methyl (*E*)-3-(benzofuran-2-yl)acrylate (4b):[7] pale yellow solid; mp 88 °C; ^{1}H NMR δ 7.58 (1H, d, *J* = 8 Hz), 7.55 (1H, d, *J* = 16 Hz), 7.48 (1H, d, *J* = 8 Hz), 7.36 (1H, t, *J* = 8 Hz), 7.24 (1H, t, *J* = 8 Hz), 6.93

(1H, s), 6.58 (1H, d, *J* = 16 Hz), 3.82 (3H, s); ^{13}C NMR δ 167.11, 155.58, 152.30, 131.47, 128.35, 126.45, 123.32, 121.74, 118.51, 111.41, 111.14, 51.79; MS *m/z* 203 ([M+H]$^+$).

Methyl (*E*)-3-(1-(phenylsulfonyl)-1*H*-indol-2-yl)acrylate (4c): pale brown solid; mp 142.8 °C; ^{1}H NMR δ 8.38 (1H, d, *J* = 16 Hz), 8.22 (1H, d, *J* = 8 Hz), 7.74 (2H, d, *J* = 8 Hz), 7.53-7.49 (2H, m), 7.41-7.36 (3H, m), 7.26 (1H, d, *J* = 8 Hz), 6.98 (1H, s), 6.38 (1H, d, *J* = 16 Hz), 3.85(3H, s); ^{13}C NMR δ 166.57, 138.13, 136.28, 134.15, 133.99, 129.41, 129.35, 129.21, 126.60, 126.29, 124.41, 121.55, 120.68, 115.27, 112.37, 51.94; MS *m/z* 342 ([M+H]$^+$); IR (ATR) 1708, 1625, 1446, 1332 cm^{-1}; HR-MS Calcd. for [$C_{18}H_{15}NO_4S$+H]$^+$: 342.0795, Found : 342.0787.

Methyl (*E*)-3-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acrylate (4d):[8] white solid; mp 127.0 °C; ^{1}H NMR δ 7.80-7.77 (1H, m), 7.73 (1H, d, *J* = 16 Hz), 7.37-7.29 (3H, m), 7.18 (1H, d, *J* = 16 Hz), 3.88 (3H, s), 3.85 (3H, s); ^{13}C NMR δ 166.73, 147.88, 143.14, 136.19, 128.91, 125.05, 123.96, 123.32, 120.27, 109.67, 52.06, 29.94; MS *m/z* 217 ([M+H]$^+$).

Methyl (*E*)-3-(benzo[*d*]thiazol-2-yl)acrylate (4e):[8] white solid; mp 108.6 °C; ^{1}H NMR δ 8.08 (1H, d, *J* = 8 Hz), 7.90 (1H, d, *J* = 8 Hz), 7.88 (1H, d, *J* = 16 Hz), 7.54-7.50 (1H, m), 7.47-7.42 (1H, m), 6.82 (1H, d, *J* = 16 Hz), 3.85 (3H, s); ^{13}C NMR δ 165.98, 163.32, 153.87, 136.94, 135.21, 126.78, 126.53, 125.59, 124.04, 121.74, 52.17; MS *m/z* 220 ([M+H]$^+$).

Methyl (*E*)-3-(2,6-dichlorophenyl)acrylate (4f):[9] ^{1}H NMR δ 7.79 (1H, d, *J* = 16 Hz), 7.36 (2H, d, *J* = 8 Hz), 7.19 (1H, t, *J* = 8 Hz), 6.60 (1H, d, *J* = 16 Hz), 3.84 (3H, s); ^{13}C NMR δ 166.66, 138.32, 135.02, 132.04, 129.84, 128.80, 126.54, 51.95; MS *m/z* 231 ([M+H]$^+$).

Methyl (*E*)-3-(2,5-dichlorophenyl)acrylate (4g):[10] ^{1}H NMR δ 8.00 (1H, d, *J* = 16 Hz), 7.58 (1H, s), 7.35 (1H, d, *J* = 8 Hz), 7.27 (1H, d, *J* = 8 Hz), 6.42 (1H, d, *J* = 16 Hz), 3.78 (3H, s); ^{13}C NMR δ 166.58, 139.45, 134.28, 133.20, 133.17, 131.35, 130.94, 127.54, 121.83, 52.05; MS *m/z* 231 ([M+H]$^+$).

Typical experimental procedure for one-pot preparation of aryl or heteroaryl-bearing acrylates (6).

Methyl (*E*)-3-(pyridin-2-yl)acrylate (6d):[11] (Table 2, entry 4)

To a solution of **5d** (249 mg, 1.58 mmol) in THF (2 mL) was added *n*-BuLi (2.2 M in hexane, 0.86 mL, 1.89 mmol) at –25 °C with stirring for 30 min. To the solution was added dropwise DMF (0.15 mL, 1.9 mmol) with stirring at that temperature for 40 min, then allowed to warmed to ice-bath temperature and stirred for additional 40 min. Trimethyl phosphonoacetate (0.30 mL, 2.1 mmol) was added with stirring at ice-bath temperature and the stirring was continued for 1 h. Aqueous 5% ammonium acetate (8 mL) was added and the mixture was extracted with EtOAc (20 mL). The organic layer was washed with 5% sodium acetate aq. (8 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The residual oil was subjected to column chromatography (silica gel) to give **6d** (174 mg, 68%) as a yellow oil.

^{1}H NMR δ 8.66 (1H, d, *J* = 4 Hz), 7.73-7.67 (1H, m), 7.69 (1H, d, *J* = 16 Hz), 7.42 (1H, d, *J* = 8 Hz), 7.28-7.25 (1H, m), 6.93 (1H, d, *J* = 16 Hz), 3.82 (3H, s); ^{13}C NMR δ 167.23, 152.95, 150.19, 143.57, 136.76, 124.25, 124.23, 122.00, 51.84; MS *m/z* 164 ([M+H]$^{+}$).

Methyl cinnamate (6a):[12] ^{1}H NMR δ 7.70 (1H, d, *J* = 16 Hz), 7.54-7.52 (2H, m), 7.39-7.38 (3H, m), 6.44 (1H, d, *J* = 16 Hz), 3.81 (3H, s); ^{13}C NMR δ 167.44, 144.88, 134.44, 130.30, 128.91, 128.09, 117.86, 51.70; MS *m/z* 163 ([M+H]$^{+}$).

Methyl (*E*)-3-(4-methoxyphenyl)acrylate (6b):[12] ^{1}H NMR δ 7.65 (1H, d, *J* = 16 Hz), 7.47 (2H, d, *J* = 8 Hz), 6.90 (2H, d, *J* = 8 Hz), 6.31 (1H, d, *J* = 16 Hz), 3.83 (3H, s), 3.79 (3H, s); ^{13}C NMR δ 167.78, 161.44, 144.54, 129.75, 127.19, 115.34, 114.37, 55.40, 51.58; MS *m/z* 193 ([M+H]$^{+}$).

Methyl (*E*)-3-(2-methoxyphenyl)acrylate (6c):[13] ^{1}H NMR δ 8.00 (1H, d, *J* = 16 Hz), 7.50 (1H, d, *J* = 8 Hz), 7.36-7.33 (1H, m), 6.98-6.90 (2H, m), 6.53 (1H, d, *J* = 16 Hz), 3.88 (3H, s), 3.80 (3H, s); ^{13}C NMR δ 167.93, 158.39, 140.28, 131.48, 128.93, 123.44, 120.72, 118.37, 111.18, 55.49, 51.57; MS *m/z* 193 ([M+H]$^{+}$).

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