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Base-catalyzed condensation of β-bromovinylaldehydes with β-ketoesters followed by water-mediated cyclization and aromatization: one-pot access to substituted benzene derivatives

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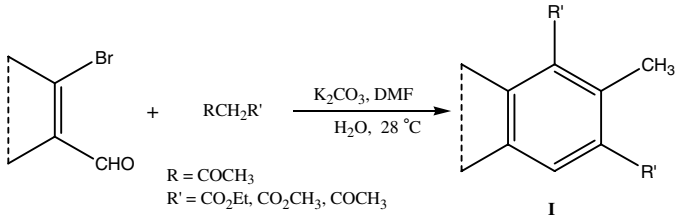
Abstract—A simple, convenient, one-pot synthetic approach towards substituted benzene derivatives using base-catalyzed condensation of β-bromovinylaldehydes with β-ketoesters followed by water-mediated cyclization and aromatization has been developed.

1. Introduction

The construction of carbocyclic skeletons is a fundamental and significant process in organic synthesis. Most annulation approaches use transition metal catalyzed reactions as a key step for the synthesis of many pharmacologically and biologically active compounds.[1] The Knoevenagel condensation has proved to be a widely employed method for carbon–carbon bond formation with numerous applications in the synthesis of fine chemicals[2] and carbocyclic compounds of biological significance.[3] Recent studies have shown that such condensations can also be performed in aqueous media at room temperature.[4] Efficient procedures for the direct formation of C–C bonds via condensation of vinyl haloaldehydes with active methylene compounds are relatively uncommon. Palladium-catalyzed aromatization via tandem Heck and aldol reactions have emerged as useful methodologies for the synthesis of substituted benzene derivatives.[5]

Palladium-catalyzed cyclization reactions have also been reported for the synthesis of cyclic compounds from *o*-halo aromatics.[6–8]

Attempts to substitute the highly reactive halogen atoms of 2-halovinylaldehydes with active methylene compounds have met with limited success. The mechanism, scope and limitation of such reactions in most cases are poorly understood. In connection with our ongoing interest in the application of bromoaldehydes[9] for the synthesis of benzene derivatives,[10] we report herein a simple and efficient one-pot protocol for the synthesis of trisubstituted, fused, benzene derivatives via condensation and aromatization of various bromoaldehydes with active methylene compounds facilitated by water, typically at room temperature (27–29 °C). The resulting aromatic products are usually functionalized[11] and this process should find considerable application for the synthesis of substituted aromatic rings. The substrates that are prone to hydrolysis, such as compounds containing



Scheme 1.

Keywords: Condensation; Aromatization; Cyclization.
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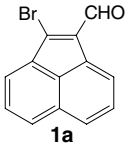
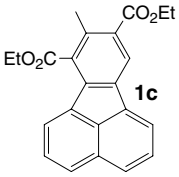
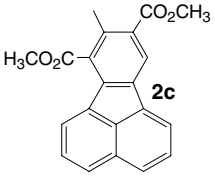
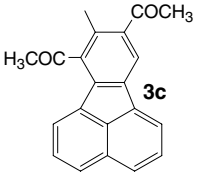
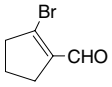
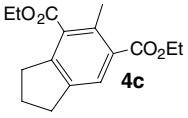
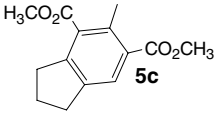
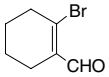
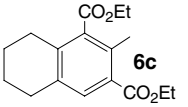
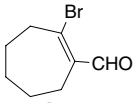
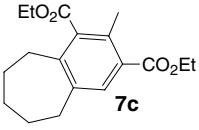
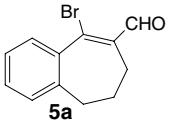
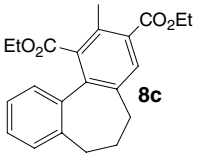
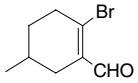
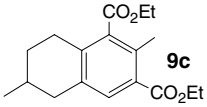
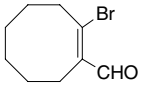
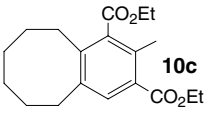
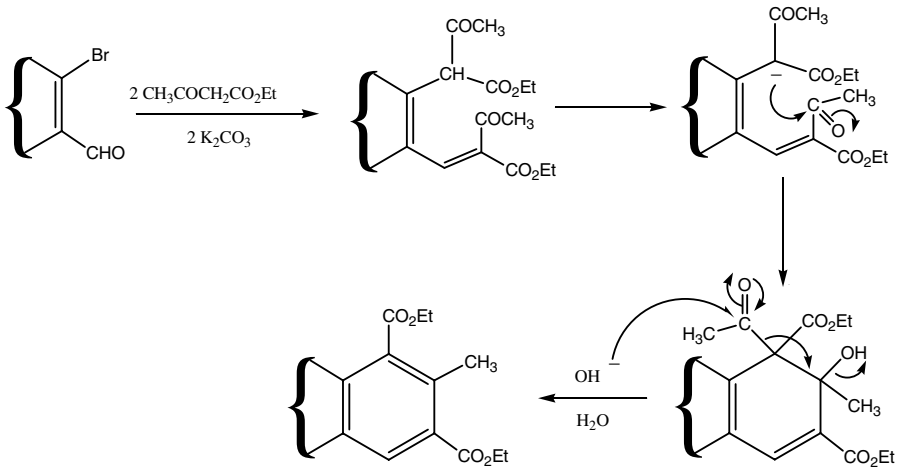
Table 1. Condensation of β-bromovinylaldehydes with β-ketoesters[a]

Entry	Substrates	β-Ketoesters	Products	Time (h)	Yield[b] (%)
1	 **1a**	$CH_3COCH_2CO_2Et$ **1b**	 **1c**	5	45
2	**1a**	$CH_3COCH_2CO_2CH_3$ **2b**	 **2c**	7	40
3	**1a**	$CH_3COCH_2COCH_3$ **3b**	 **3c**	7	50
4	 **2a**	**1b**	 **4c**	8	55
5	**2a**	**2b**	 **5c**	8	60
6	 **3a**	**1b**	 **6c**	9	50
7	 **4a**	**1b**	 **7c**	10	60
8	 **5a**	**1b**	 **8c**	6	48[c]
9	 **6a**	**1b**	 **9c**	8	52
10	 **7a**	**1b**	 **10c**	12	70

[a] Reaction conditions: β-bromovinylaldehyde (1 mmol), β-ketoester (2 mmol), K_2CO_3 (2 mmol), DMF (5 mL), 28 °C.
[b] After addition of 20 mL of water to the reaction mixture and stirring for 10 h. All compounds gave satisfactory ^1H NMR, ^{13}C NMR and MS spectroscopic data.
[c] The reaction mixture containing **5a** was heated to 70 °C initially and water was added after 6 h.

ester functionalities, were tolerated under the reaction conditions.

When 1 mmol of bromovinylaldehyde and 2 mmol of β-ketoester were stirred at room temperature in DMF in



Scheme 2. Possible mechanism of the base-catalyzed condensation followed by cyclization with ethyl acetoacetate in the presence of water.

presence of potassium carbonate followed by treatment with water, trisubstituted, fused, aromatic compounds were obtained in moderate yields (Scheme 1, Table 1).

For 3-bromo-3-phenylpropenal, one molecule of β-keto-ester condenses with the aldehyde and the bromo group remains intact. Both the cis and trans isomers (1:1) are formed in this case.

The reaction may follow the pathway outlined in Scheme 2. Ethyl acetoacetate may condense with the aldehyde and replace the vinylic bromide. The resulting product may then cyclize and aromatize after the loss of acetic acid and dehydration. We have been unable to isolate the intermediate before adding water to the reaction mixture, possibly due to decomposition after being isolated from the reaction mixture.

We performed the reaction in various solvents and obtained different yields (Table 2).

During our studies of this method, we obtained an interesting result on varying the solvent system. When 2-bromocyclopent-1-encarbaldehyde was treated with ethyl acetoacetate and potassium carbonate in a solvent system containing DMF and water (1:1), compound **II**[12] was unexpectedly obtained in 52% yield (Scheme 3).

A plausible mechanism for the above reaction is outlined below (Scheme 4).

In summary, we have outlined a simple and efficient base-catalyzed cyclization and aromatization for the synthesis of fused trisubstituted aromatic compounds.

Table 2. Condensation of **4a** with ethyl acetoacetate in various solvents[a]

Entry	Solvents	Time (h)	Yield[b] (%)
1	THF	11	49
2	Ethanol	13	44
3	CH_3CN	14	40

[a] Reaction conditions: **4a** (1 mmol), ethyl acetoacetate (2 mmol), K_2CO_3 (2 mmol), solvent (5 mL), rt.
[b] After addition of 20 mL of water to the reaction mixture and stirring for 10 h.

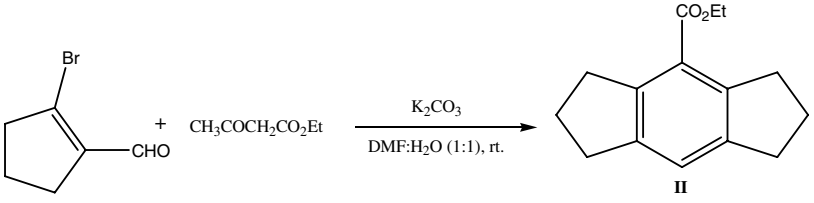
2. Typical experimental procedure

A mixture of β-bromovinylaldehyde (1 mmol), β-keto-ester (2 mmol) and K_2CO_3 (2 mmol) was taken in a two-neck flask. After the system had been flushed with argon, 5 mL of DMF was added and the reaction mixture was allowed to stir at rt and monitored by TLC. After the disappearance of starting material, 20 mL of water was added to the mixture which was stirred for 10 h. The mixture was then extracted with dichloromethane repeatedly and washed with 1 N HCl solution followed by ice cold water. Removal of the solvent after drying (anhydrous Na_2SO_4), afforded the crude product, which was chromatographed on silica (60–120 mesh).

3. Spectral data of representative compounds

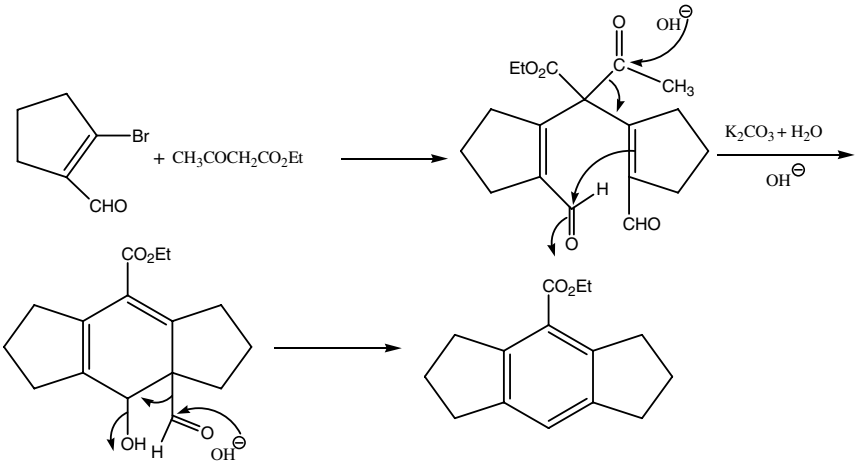
3.1. Diethyl 8-methylfluoranthrene-7,9-dicarboxylate (1c)

Yellow crystalline solid, mp 90 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42–1.52 (m, 6H), 2.66 (s, 3H), 4.44 (q, 2H,



II

Scheme 3.



Scheme 4.

$J = 7.2$ Hz), 4.61 (q, 2H, $J = 7.2$ Hz), 7.58–7.70 (m, 2H), 7.85–8.02 (m, 4H), 8.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 14.24, 17.91, 60.99, 61.63, 120.42, 122.88, 123.86, 127.07, 127.89, 127.94, 128.02, 129.65, 129.85, 130.66, 132.97, 134.09, 134.99, 135.38, 137.05, 167.47, 169.23; MS (ES+, 70 eV): $m/z = 361$ (100%) [M^++H]. Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.66; H, 5.55. Found: C, 76.42; H, 5.61.

3.2. Diethyl 5-methylindan-4,6-dicarboxylate (4c)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, 3H, $J = 7.2$ Hz), 1.38 (t, 3H, $J = 7.1$ Hz), 2.01–2.12 (m, 2H), 2.52 (s, 3H), 2.92 (q, 4H, $J = 7.6$ Hz), 4.29–4.45 (m, 4H), 7.75 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.24, 17.73, 25.04, 32.30, 32.51, 60.79, 61.03, 127.24, 129.74, 131.69, 134.77, 142.15, 146.31, 167.91, 169.03; MS (ES+, 70 eV): $m/z = 277$ (100%) [M^++H]. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.56; H: 7.24. Found: C, 69.43; H, 7.11.

3.3. Ethyl *s*-hydrindacene-4-carboxylate (II)

White amorphous solid, mp 42 °C (lit., 42–43 °C),[12] IR: 863, 1240, 1703 [lit., 864 (solitary Ar–H), 1236 (C–O–C), 1712 ($ArCOOH_2CH_3$)]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (t, 3H, $J = 7.2$ Hz), 2.05 (m, 4H), 2.86 (t, 4H, $J = 7.4$ Hz), 3.15 (t, 4H, $J = 7.4$ Hz), 4.34 (q, 2H, $J = 7.2$ Hz), 7.22 (s, 1H) [lit., δ 7.20 (s, 1H, Ar–H), 4.35 (q, $J = 7.0$ Hz, 2H, $COOCH_2$), 3.18 (t, $J = 7.0$ Hz, 4H, $2CH_2$ in positions 3 and 5), 2.80 (t, $J = 7.0$ Hz, 2H, remaining two Ar–CH_2), 2.10 (m, 4H, remaining isolated CH_2), 1.42 (t, $J = 7.0$ Hz, 3H, C–CH_3)]; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 25.5, 32.42, 33.68, 60.25, 123.85, 123.96, 143.72, 143.78, 168.02. Anal. Calcd for $C_{15}H_{18}O_2$ (230.3): C, 78.22; H, 7.88. Found: C, 78.22; H, 8.08 [lit. found: C, 78.16; H, 7.92].

Acknowledgement

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