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Synthesis of substituted benzene derivatives by homo- and hetero-coupling of 2-bromobenzaldehyde and bromovinylaldehydes followed by McMurry coupling

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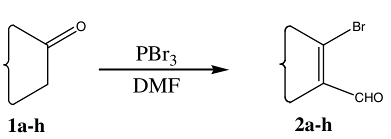
Abstract—A convenient synthetic approach to substituted benzene derivatives by modified Ullmann cross-coupling of 2-bromobenzaldehyde and bromovinylaldehydes followed by intramolecular McMurry coupling has been developed.

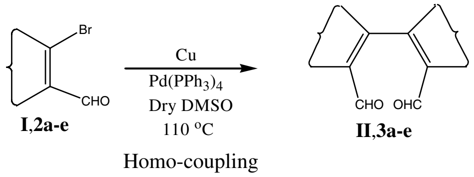
We have been interested in the synthesis of heterocyclic compounds from 2-chlorovinylaldehydes[1–3] and were interested in developing the methodology for the synthesis of substituted benzene derivatives from bromovinylaldehydes.[4]

Thus, when ketomethylene compounds **1a**–**h** were treated with PBr_3 in DMF, bromovinylaldehydes **2a**–**h**[5] were produced (Scheme 1). Treatment of 2-bromobenzaldehyde **I** and bromovinylaldehydes **2a**–**e** with an equivalent of Cu powder and 10 mol % of $Pd(PPh_3)_4$ in anhydrous DMSO with heating at 110 °C afforded homo bis-aldehydes **II** and **3a**–**e**[6] (Scheme 2) by modified Ullmann reaction[7] (Table 1 and Fig. 1).

When 2-bromobenzaldehyde **I** and bromovinylaldehydes **2b**,**c**,**d**,**f**,**g**,**h** were reacted, only cross-coupled bis-aldehydes **3f**–**k** were isolated under similar conditions to those of the homo-coupling reaction at 85 °C (Scheme 3 and Table 2). Raising the temperature from 85 °C to 110 °C led to a mixture of homo- and hetero-coupled bis-aldehydes. Thus, we had determined the optimum temperature for preparing cross-coupled products.



Scheme 1.



Scheme 2.

An interesting observation was noticed during the homo-coupling of 2-bromo-3,4-dihydronaphthalene-1-carbaldehyde **2c** as well as during its hetero-coupling with **I**, which unexpectedly produced aromatized products **3c** and **3j** (Table 1, entry 4 and Table 2, entry 5). These bis-aldehydes upon treatment with $TiCl_4$ and Zn dust, underwent intramolecular McMurry coupling[9] to generate substituted benzenes **4a**–**k** (Scheme 4, Fig. 2 and Table 3).

In conclusion we have developed a methodology for the synthesis of various substituted benzenes starting from ketomethylene compounds. Our method provides short reaction times and good yields. The temperature for homo-coupling was optimized at 110 °C and that for hetero-coupling was 85 °C. Compound **4b** is an important intermediate for the synthesis of helicenes.[4e]

Keywords: Ullmann reaction; McMurry coupling.

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Table 1. Homo-coupling of various bromovinylaldehydes catalyzed by palladium(0) at 110 °C

Entry	Bromovinylaldehyde	Product[a]	Time (h)	Yield (%)
1	2-Bromobenzaldehyde **I**	**II**[6b]	6	65
2	2-Bromoacenaphthylene-1-carbaldehyde **2a**	**3a**	4	65
3	1-Bromo-3,4-dihydronaphthalene-2-carbaldehyde **2b**	**3b**	5	60
4	2-Bromo-3,4-dihydronaphthalene-1-carbaldehyde **2c**	**3c**	4	56
5	3-Bromo-3-phenylpropenal **2d**	**3d**	4	58
6	5-Bromo-8,9-dihydro-7*H*-benzocycloheptene-6-carbaldehyde **2e**	**3e**	4	60

[a] See Figure 1 for the structures of the homo-coupled products.

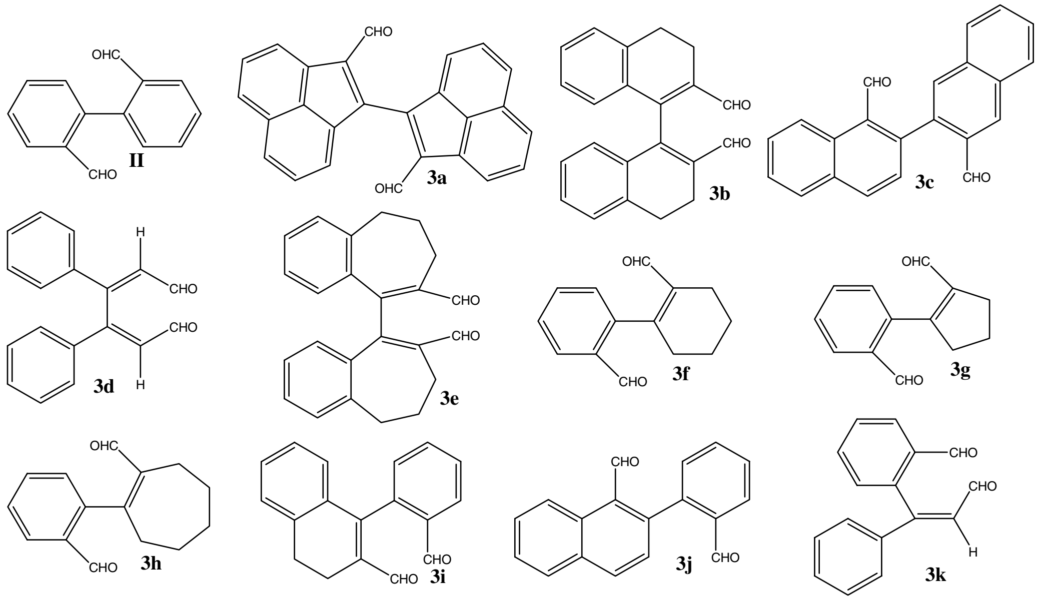
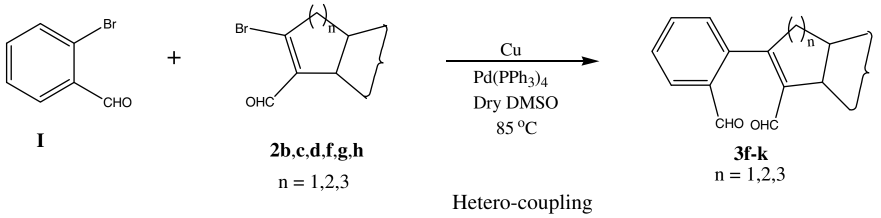


Figure 1. Bis-aldehydes **II** and **3a**–**e** were produced by homo-coupling and **3f**–**k** by the hetero-coupling reaction between 2-bromo-benzaldehyde **I** and bromovinylaldehydes **2b**,**c**,**d**,**f**,**g**,**h**.



Scheme 3.

Table 2. Hetero-coupling of various bromovinylaldehydes catalyzed by palladium(0) at 85 °C

Entry	Bromovinylaldehyde[a]	Product[b]	Time (h)	Yield (%)
1	2-Bromocyclohex-1-enecarbaldehyde **2f**	**3f**	4	65
2	2-Bromocyclopent-1-enecarbaldehyde **2g**	**3g**	3.5	65
3	2-Bromocyclohept-1-enecarbaldehyde **2h**	**3h**	3	65
4	1-Bromo-3,4-dihydronaphthalene-2-carbaldehyde **2b**	**3i**	4.5	60
5	2-Bromo-3,4-dihydronaphthalene-1-carbaldeyde **2c**	**3j**[6c]	4	58
6	3-Bromo-3-phenylpropenal **2d**	**3k**	5	62

[a] 2-Bromobenzaldehyde **I** was used as the second coupling partner.

[b] See Figure 1 for the structures of the hetero-coupled products.

Typical experimental procedure for the homo and hetero cross-coupling of bromovinylaldehydes: A magnetically stirred mixture of appropriate bromovinylaldehyde (0.81 mmol), copper powder (8.2 mmol), and $Pd(PPh_3)_4$ (10 mol %) in dry DMSO (6 mL) was degassed for 15 min, and then heated at 110 or 85 °C (depending upon homo- or hetero-coupling) for 4–6 h under a nitrogen atmosphere. It was then cooled to room tempera-

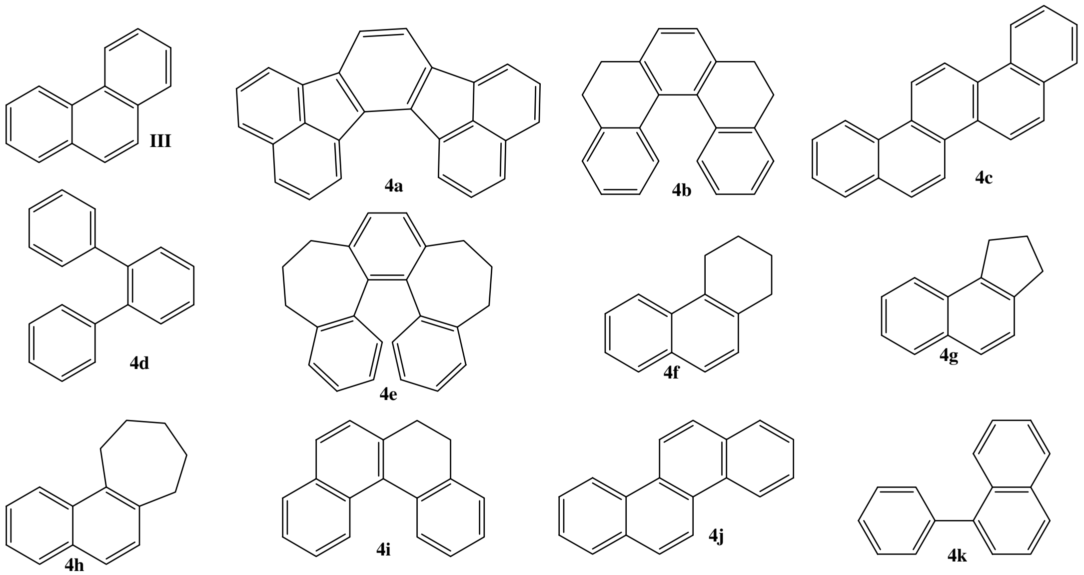
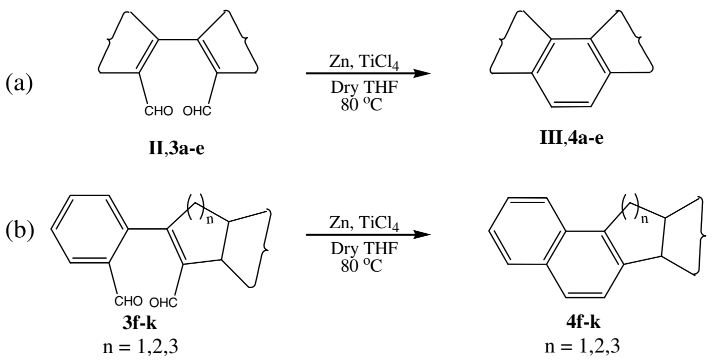


Figure 2. Substituted benzene derivatives **III** and **4a**–**k** produced by intramolecular McMurry coupling of bis-aldehydes **II** and **3a**–**k**.



Scheme 4.

ture and diluted with ethyl acetate (80 mL). The resulting mixture was filtered through a pad of celite and the residue thus retained was washed with ethyl acetate (30 mL). The combined filtrates were washed with water (2 × 150 mL), brine (150 mL) and then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude product, which often solidified without further purification. In some cases column chromatography (silica gel—ethyl acetate/pet ether elution) and concentration of the appropriate fractions afforded the coupling products.

Table 3.

Entry	Bis-aldehyde	Product[a]	Yield (%)
1	**II**	**III**	67
2	**3a**	**4a**[8a]	56
3	**3b**	**4b**[4e]	62
4	**3c**	**4c**[4a]	57
5	**3d**	**4d**[8b]	60
6	**3e**	**4e**[8c]	58
7	**3f**	**4f**[8d]	65
8	**3g**	**4g**[8e]	65
9	**3h**	**4h**[8e]	65
10	**3i**	**4i**[4b]	62
11	**3j**	**4j**[8f]	58
12	**3k**	**4k**[8g]	60

[a] All products have been characterized by spectroscopic data.

Typical experimental procedure for McMurry coupling of bis-aldehydes: To an ice cooled suspension of active zinc dust (4.9 mmol) in THF (6 mL) under argon, $TiCl_4$ (0.3 mL) was injected slowly. The mixture was then refluxed for 2 h and again cooled to 0 °C. To this, a solution of bis-aldehyde (0.53 mmol) in THF (2 mL) was added dropwise with stirring at 0 °C for a further 30 min, then the reaction was allowed to attain room temperature gradually. Finally it was refluxed for 2 h at 80 °C. The reaction mixture was cooled, poured into an ice-cold saturated potassium carbonate solution and extracted with dichloromethane. The organic layer was washed thoroughly with water and brine several times, dried (anhydrous Na_2SO_4) and then the solvent was removed to afford the product.

Selected spectroscopic data—Compound **3c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.39–7.44 (d, 2H, $J = 8.44$ Hz), 7.56–7.72 (m, 4H), 7.86–7.89 (d, 2H, $J = 4.8$ Hz), 7.95–7.96 (d, 2H, $J = 2.08$ Hz), 9.28–9.32 (d, 2H, $J = 8.52$ Hz) 10.22 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 125.78, 127.40, 128.50, 128.60, 129.58, 129.94, 130.37, 133.48, 133.85, 145.03, 192.80. Anal. Calcd for $C_{22}H_{14}O_2$: C: 85.15, H: 4.54. Found: C: 85.25, H: 4.52.

Compound **3g**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.74–2.96 (m, 6H), 7.25–7.31 (dd, 1H, $J = 1.34$ Hz, $J = 1.34$ Hz), 7.52–7.67 (m, 2H), 7.95–7.99 (dd, 1H, $J = 1.38$ Hz, $J = 1.38$ Hz), 9.46 (s, 1H), 10.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 22.34, 30.69, 42.08, 129.39, 129.95, 131.69, 133.84, 134.16, 137.82, 142.45, 161.29, 189.81, 190.79. Anal. Calcd for $C_{13}H_{12}O_2$: C: 77.99, H: 6.04. Found: C: 77.82, H: 6.06.

Compound **4g**: ^{1}H NMR ($CDCl_3$, 200 MHz)[8f] δ: 2.20–2.32 (m, 2H), 3.06–3.14 (t, 2H, $J = 7.35$ Hz), 3.21–3.29 (t, 2H, $J = 7.45$ Hz), 7.37–7.51 (m, 3H), 7.65–7.69 (d, 1H, $J = 8.28$ Hz), 7.81–7.86 (t, 2H, $J = 7.9$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 24.52, 31.02, 33.76, 123.26, 124.24, 124.58, 125.77, 126.58, 128.31, 130.45, 132.47, 139.37, 140.92. Anal. Calcd for $C_{13}H_{12}$: C: 92.85, H: 7.15. Found: C: 92.90, H: 7.25.

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