Table III. Rate Constants, k_{obsd} (M^{-1} s^{-1}), for the Reaction of Nitrosobenzene with α-Oxo Acids

				in HCl at pH 0.6		in aqueous AcOH	
α-oxo acid	R	σ^* [a]	E_s [a]	log k_{obsd}	log k_{calcd} [b]	log k_{obsd}	log k_{calcd} [c]
1a	H	0.49	1.24	−1.201	−1.196	−2.456	−2.455
1b	CH_3	0	0	−2.114	−2.155	−3.276	−3.288
1c	C_2H_5	−0.10	−0.07	−2.268	−2.233	−3.367	−3.357
1d	C_6H_5	0.60	−2.55	−3.602	−3.600	−4.509	−4.509

[a] The σ^* (polar substituent constant) and E_s (steric substituent constant) values are from ref 30 and 31, respectively. [b,c] Calculated using eq 3 (for b) and eq 4 (for c) using parameters determined by the least-squares method.

Table IV. Hydrolysis Rate Constants, k_H (s^{-1}), for N-Phenylhydroxamic Acids in HCl at pH 0.6

hydroxamic acid	R[a]	log k_H	log $k_{H(calcd)}$ [b]
8a	H	−3.721	−3.718
8b	CH_3	−4.456	−4.481
8c	C_2H_5	−4.553	−4.532
8d	C_6H_5	−5.865	−5.864

[a] The σ^* and E_s values used are shown in Table III. [b] Calculated with eq 5 using parameters determined by the least-squares method.

sidered to proceed via an initial nucleophilic attack by nitroso nitrogen on the carbonyl carbon of an α-oxo acid and/or a protonated one. The fact that better correlations have been found using σ^+ values (see Figure 3) indicates the formation of a transient adduct (14), which should be stabilized by an electron-donating para substituent through a resonance effect. The adduct is then converted to the corresponding N-arylhydroxamic acid through decarboxylation, presumably a driving force for the forward reaction. That ethyl pyruvate does not react with nitrosobenzene (data not shown) is explained by the low ability for the corresponding adduct to decarboxylate. It is reasonable to suggest that the initial nucleophilic attack, which is affected by substituents R and X (see Scheme I) through their polar (minor) and steric (major) effects, is the rate-determining step for this overall reaction.

In conclusion, our method should be applicable to the synthesis of various N-arylhydroxamic acids.

Rates and Regioselectivities of the Palladium-Catalyzed Ethynylation of Substituted Bromo- and Dibromobenzenes

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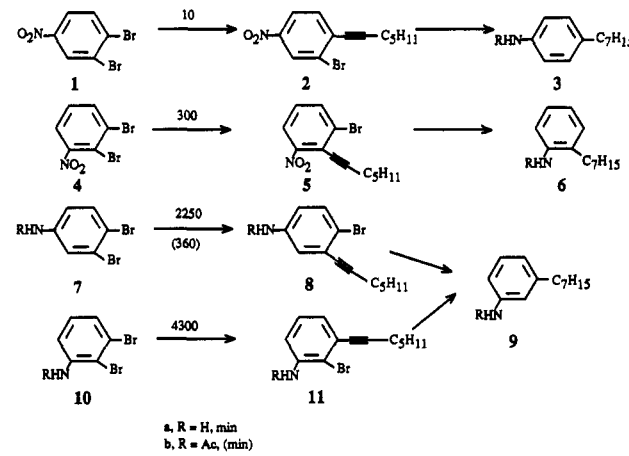
The Pd(0)/Cu_2Br_2-catalyzed ethynylation of 1,2-dibromo-4-nitro- and 1,2-dibromo-3-nitrobenzenes provide rapidly the product in which the bromine para or ortho to the nitro group is displaced, whereas the corresponding dibromoacetamidobenzenes provide the product of meta displacement slowly. Investigation of the rates of a series of para-substituted bromobenzenes indicates that the reaction is zero-order with respect to the heptyne and bromobenzene concentration, with a Hammett ρ value of 2.8.

Introduction

The palladium-catalyzed cross-coupling reactions of aryl halides[1,2] and aryl triflates[3] with alkyl, vinyl, acetylenic, and aryl tin reagents have been shown to proceed in high yields under mild conditions. Also, halopyridine derivatives have been shown[4,5] to undergo a regioselective palladium-catalyzed coupling reaction with terminal acetylenes and aryl zinc halides. We recently described[6] a simple entry into the benzene-o-diyne system similar to the ene–diyne system of several members of a related class of DNA damaging agents, esperamicins[7] and calicheamicins[8] using the Pd(0)-catalyzed coupling of o-dibromobenzene with various terminal acetylenes. The second

Scheme I



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Pd(0)-catalyzed ethynylation proceeded at approximately one-tenth the rate of the initial ethynylation. This result prompted us to study the effect of substituents on the rate and regioselectivity of the ethynylation reaction.

Results and Discussion

Nitration of *o*-dibromobenzene[9] gave 4-nitro- and 3-nitro-1,2-dibromobenzene (**1** and **4**) as major (84%) and minor (16%) products (Scheme I). Reaction of **1** with 1-heptyne in NEt_3 as solvent in the presence of 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2 at room temperature for 5 h gave the para substitution product **2** (92%) as the sole detectable product. At reflux, the reaction took 10 min. That the reaction took place para to the nitro group was suggested by the ^1H NMR spectrum of **2** and by reduction with 5% Pd/C (10 equiv H_2/EtOH) to *p*-*n*-heptylaniline (**3a**) (75%) and acetylation of **3a** to **3b**. The latter products showed AB quartets at δ 6.60 and 6.95 characteristic of a para-substituted benzene. In contrast, 4-amino- and 4-acetamido-1,2-dibromobenzene (**7a** and **7b**) underwent the same reaction in boiling NEt_3 much more slowly (38 and 6 h respectively), providing meta substitution product **8a** (70%) and **8b** (78%). Acetylation of **8a** gave **8b**. Catalytic hydrogenation of **8a** with 5% Pd/C in ethanol gave *m*-*n*-heptylaniline (**9a**) (75%), which was acetylated to **9b**. The ^1H NMR spectra of **8a** and **8b** were consistent with the structure assigned.

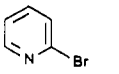
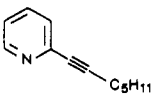
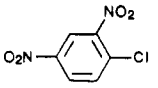
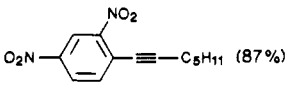
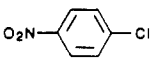
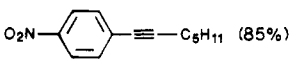
A similar reaction with 3-amino-1,2-dibromobenzene (**10a**) also gave slowly (3 days) the product of meta substitution, **11a** (72%). Formal proof that this product had the structure assigned was based on the fact that catalytic hydrogenation (5% Pd/C in EtOH), followed by acetylation, gave *m*-*n*-heptylacetanilide (**9b**), which was identical in all respects with **9b** obtained from **8a**. Submitting 3-nitro-1,2-dibromobenzene (**4**) to the standard ethynylation conditions gave the ortho substitution product **5** (82%) after 5 h at reflux. The fact that it reacted 30 times more slowly than **1** probably reflects steric hindrance of the bromine that undergoes substitution. Reduction as described provided *o*-*n*-heptylaniline (**6a**), which was isomeric (MS) but different from **3a** and **9a** (^1H NMR). This selectivity should be very useful for preparing substituted aromatic compounds which are not easily available by other reactions.

Due to the remarkable rate differences observed in the conversion of **1** → **2** as compared to **7a** → **8a**, we undertook a systematic study of the effect of para substituents on the rate of substitution of halides by acetylenes.

It had been noted by Fitton and Rick[10] that the order of reactivity of aryl halides with $Pd(0)(PPh_3)_4$ was PhI > PhBr > PhCl and 4-$NO_2C_6H_4Cl$ > 4-CNC_6H_4Cl > 4-$PhCOC_6H_4Cl$ > PhCl, with products isolated in 95–0% yield at temperatures ranging from 80 to 135 °C. Cassar[11] showed that halobenzenes and substituted halobenzenes underwent a Pd-catalyzed ethynylation in the presence of NaOMe, at reaction temperatures of 40–100 °C and reaction times of 3–8 h. Dieck and Heck[12] carried out similar reactions at 100 °C, the reaction time ranging from 0.5 to 2.25 h. Sonogashira et al.[13] used the $Pd(PPh_3)_2Cl_2$[14]/CuI system at room temperature to provide a number of arylacetylenes, after 3–6 h.

Table I. Aryl Bromides Bearing Substituents Reacted at Room Temperature or in Boiling Triethylamine with 1-Heptyne[a]

4-X-C_6H_4Br → 4-X-C_6H_4-C≡C-C_5H_{11}

X	time, min: 20 °C	time, min: 90 °C	yield,[b,c] %
NO_2	360	<3	95
CN	540	10	100
CHO	840	15	90
$COOCH_3$	1200	20	92
COOH	1680	30	80
Cl	1680	30	81
CH_3		80	75
H		90	75
CH_3O		105	62
NH_2		480	88
	180	20	 (81%)
	420	25	 (87%)
		1440	 (85%)

[a] All reactions are done in presence of 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2 under N_2. [b] The yields are reported after purification by column chromatography. [c] All compounds had correct and consistent spectral properties by GC/MS, ^1H NMR, and HRMS.

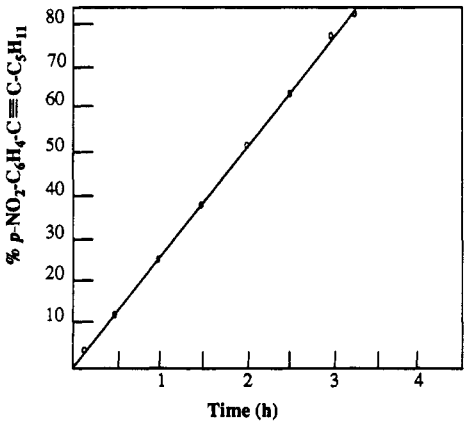


Figure 1. Reaction of *p*-bromonitrobenzene with 1-heptyne in NEt_3 under N_2 at 20 °C catalyzed by 2 mol % $Pd(PPh_3)_4$–3 mol % Cu_2Br_2.

Aryl bromides (1 equiv) bearing a variety of substituents were reacted at room temperature or in boiling triethylamine with 1-heptyne (1 equiv) and 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2.[15] The endpoint of the reaction was determined by TLC (disappearance of 4-X-C_6H_4Br). As can be seen from Table I, the reaction proceeds 30–120 times more rapidly at 90 °C than at room temperature, with differences of rates of ≈100 between *p*-NO_2 (instantaneous at 90 °C) vs *p*-OMe (1.75 h) or *p*-NH_2 (8 h) substitution.

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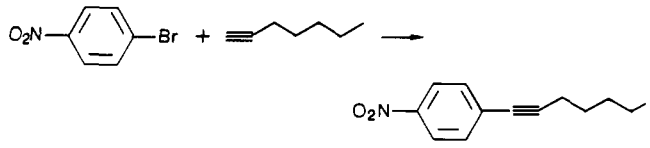
(14) It was found that tetrakis(triphenylphosphine)palladium(0) could just as well catalyze the substitution reaction in triethylamine without any added advantage over the palladium(II) precatalyst.
(15) Copper bromide (99.999%, Gold Label) gave identical results as copper iodide.

Table II. Observed Reaction Rates with Respect to Varying Amounts of Catalyst in the Reaction (at 20 °C)[a-c]



entry	$Pd(PPh_3)_4$ mol %	Cu_2Br_2 mol %	rate, M min^{-1}	relative rate
1	2	0	no reaction at 20 °C	
2	2	1	3.2×10^{-6}	1
3	2	2	1.7×10^{-5}	5.2
4	2	3	1.0×10^{-3}	325
5	2	4	8.8×10^{-6}	2.7
6	4	6	2.1×10^{-3}	650

[a] Concentration of each substrate is 3.6 mmol in 15 mL of NEt_3. Reactions were conducted under N_2. [b] The rates of reactions were determined by monitoring GC responses for product formation. [c] Concentration of product was determined by internal standard (diphenylmethane) method.

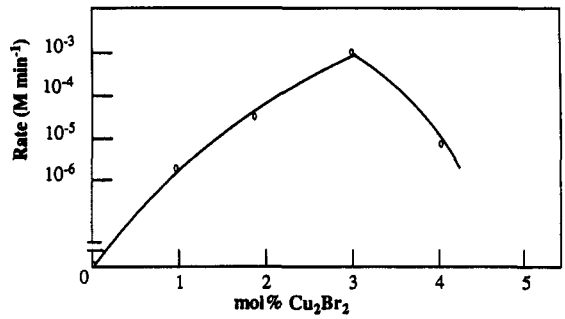
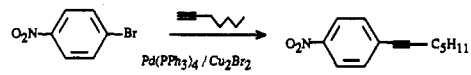


Figure 2. Rate of reaction versus concentration of Cu_2Br_2 (mol %).

The reaction of *p*-bromonitrobenzene with 1-heptyne (eq 1) in the presence of $Pd(PPh_3)_4$ (2 mol %) and Cu_2Br_2 (3 mol %) is observed to be zero-order both with respect to *p*-bromonitrobenzene and 1-heptyne (Figure 1).[16]



(1)

This has been observed by Stille and Milstein[17] in their synthesis of ethylbenzene by a Pd-catalyzed reaction of benzyl bromide and tetramethyltin. The reaction is zero-order both with respect to benzyl bromide and tetramethyltin.

It is known that the reaction of bromo- or iodoarenes with acetylenes in the presence of copper(I) iodide and a palladium/triphenylphosphine complex give acetylenic arenes.[6,13,18] However, the detailed mechanism of the reaction or the exact role of copper(I) iodide has yet to be determined. This being the case, we decided to study the reaction rates with respect to varying amounts of catalysts in the coupling reaction of *p*-bromonitrobenzene and 1-heptyne. The results are summarized in Table II and Figure 2.

It was found that when Cu_2Br_2 was not added (entry 1), there was no evidence of product formation at room temperature. As the percentage of Cu_2Br_2 was increased from 1 mol % to 3 mol % (entried 2–4), the rate increased, and then decreased at 4 mol % (entry 4). The optimum $Pd(PPh_3)_4/Cu_2Br_2$ ratio was found to be 2/3. It is interesting to note that the relative rate doubles (325 to 650) as the catalyst concentration was increased from 2 mol % $Pd(PPh_3)_4$/3 mol % Cu_2Br_2 to 4 mol % $Pd(PPh_3)_4$/6 mol % Cu_2Br_2.

Table III. Reaction Rates of Substituted Bromobenzenes with 1-Heptyne Catalyzed By 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2[a-c]

substituent	rate, M min^{-1}	relative rate
p-NO_2	1.0×10^{-3}	1800
p-CN	7.0×10^{-4}	1190
p-CHO	1.8×10^{-4}	313
H	2.2×10^{-5}	38
p-OCH_3	5.8×10^{-7}	1

[a] In NEt_3, under N_2, at 20 °C. [b] The rates of reactions were determined by monitoring GC responses for product formation. [c] Concentration of product was determined by internal standard (diphenylmethane) method.

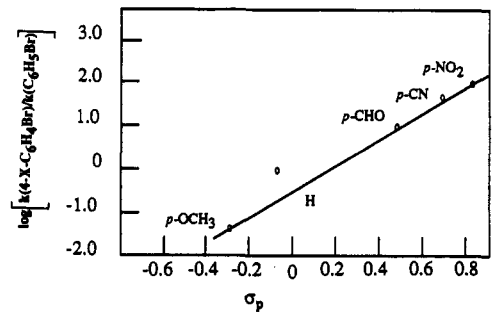


Figure 3. Hammett plot of the reaction *p*-X-C_6H_4Br with 1-heptyne in NEt_3 in presence of 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2 under nitrogen at 20 °C.

The reaction clearly is accelerated by electron-withdrawing substituents on the aryl bromide as was noted by Fitton and Rick.[10] The relative rates (Table III) obtained for various para substituents have been plotted against the Hammett σ values (Figure 3)[19] for the coupling of *p*-X-C_6H_4Br and 1-heptyne in presence of 2 mol % $Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2. The ρ value is 2.8, indicating a relatively high sensitivity to substituent effects for electron-withdrawing groups. Similar effects have been observed in the oxidative addition reaction of bromobenzenes with tetramethyltin catalyzed by benzylchlorobis(triphenyl)palladium(II)[15] and in the oxidative addition reaction of aryl halides to tris(triphenylphosphine)nickel(0).[20] In view of the similarity between the substituent effect on oxidative addition and on the reaction between organic halides and acetylene (1-heptyne) catalyzed by Pd(0)/Cu_2Br_2, the oxidative addition of the halide to palladium most likely is rate-determining. This is supported by the large difference in reactivity observed for *p*-bromonitrobenzene (<3 min at 90 °C, Table I) and *p*-chloronitrobenzene (1440 min at 90 °C, Table I).

We have measured relative ratios of formation of 3-(1-heptynyl)benzonitrile and 4-(1-heptynyl)benzonitrile by carrying out competitive reactions with *m*-bromobenzonitrile and *p*-bromobenzonitrile in the presence of 1-heptyne (1 equiv) in NEt_3 using 2 mol % ($Pd(PPh_3)_4$ and 3 mol % Cu_2Br_2 as catalyst in order to determine the meta

(16) The amount of product formation in the reaction between 1-heptyne and 4-bromonitrobenzene shown in Figure 1 was measured by GC responses using internal standard (diphenylmethane) method at every 30-min interval.

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(19) The σ_p values are based on Exner, O. In *Correlation Analysis in Chemistry*, Chapman, N. B., Shorter, J., Ed.; Plenum Press: New York, 1978; Chapter 10.

(20) Foa, M.; Cassar, L. *J. Chem. Soc., Dalton Trans.* **1975**, 2572.

and para substituent effect. The relative ratio of meta/para product formation was found to be 3:17.

The use of Cu_2Br_2 in the Pd(0) coupling reaction of aryl bromide with an acetylene increases the reaction rate, and another advantage in its use is the ability to easily purify the products without any traces of PPh_3 contamination. In absence of Cu_2Br_2 the $Pd(PPh_3)_4$ catalyst gives off 2 mol of PPh_3 in solution.

Experimental Section

The ^1H NMR spectra (200 MHz) were recorded on a Varian XL-200 instrument using tetramethylsilane as internal standard, in deuteriochloroform as solvent. The chemical shift (δ) and coupling constant (J) data are quoted in ppm and hertz, respectively. Gas chromatographic analysis utilized a Hewlett-Packard 5890 instrument operated with a fused silica capillary column (25 m × 0.2 mm) and a flame ionization detector at 250 °C with an injection port at 250 °C. The GC was run using a temperature program set from 100 to 200 °C with a rate of 10 °C/min, and helium gas was used as carrier gas. The response of the detector to reaction products and to the reference standard (diphenylmethane) was examined and calibration graphs constructed. Areas under the peaks were determined with a 3392A Hewlett-Packard integrator. Mass spectra were recorded on MP 5884A or LKB 9000 spectrometers, ion source 250 °C and 70 eV electron impact, direct inlet: m/e (assignment). GC/MS were performed on a Varian 3500 capillary gas chromatograph with a Finnigan Mat Ion Trap detector. Thin-layer chromatography was performed on silica gel (Kieselgel 60F 254) aluminum-backed plates. Flash chromatography was done using silica gel (Kieselgel 60, 230–400 mesh). The ^1H NMR of the compounds indicated a purity of at least 95%, unless otherwise stated. Purity of volatile compounds were ascertained by GC or LRMS with specific ion monitoring. Generally, compounds isolated were oils unless otherwise indicated. All solvents were reagent grade unless otherwise stated. Triethylamine was refluxed and distilled over calcium hydride. Melting points were determined on a Gallenkamp block and are uncorrected.

General Procedure for Coupling 1-Heptyne with Organic Halides. To a solution of 3.6 mmol of the organic halide and 3.6 mmol of 1-heptyne in 15 mL of triethylamine was added $Pd(0)(PPh_3)_4$ (0.072 mmol, 83 mg) and Cu_2Br_2 (0.108 mmol, 31 mg). The dark yellow solution was stirred under nitrogen at 20 °C until completion of reaction by TLC. The solution was concentrated and diluted with diethyl ether (100 mL), and the ether solution was washed with saturated NH_4Cl (2 × 25 mL), dried over $MgSO_4$, purified by column chromatography, and analyzed by GC/MS.

Significant Characterization Data Includes: 4-Nitro-1,2-dibromobenzene (1). The yield was 84%. After recrystallization from methanol, the mp was 54.5–55 °C (lit.[9] mp 55 °C): ^1H NMR δ 7.79 (d, 1 H, J_{ortho} = 7.5 Hz, C_6H_3), 8.00 (dd, 1 H, J_{ortho} = 7.5 Hz, J_{meta} = 2.6 Hz, C_6H_3), 8.48 (d, 1 H, J_{meta} = 2.6 Hz, C_6H_3); MS m/e (rel %) a 1:2:1 triplet at 283 (3.6) ($M^{\bullet+}$), 281 (6.8) ($M^{\bullet+}$), 279 (3.8) ($M^{\bullet+}$), and 237 (2.0) ($M^{\bullet+} - NO_2^+$), 235 (4.5) ($M^{\bullet+} - NO_2^+$), 233 (2.8) ($M^{\bullet+} - NO_2^+$); HRMS m/e calcd for $C_6H_3NO_2{}^{79}Br_2$ 278.8531, found 278.8570.

1-(2-Bromo-4-nitrophenyl)heptyne (2). The coupling of 4-nitro-1,2-dibromobenzene (1) with 1-heptyne using the general coupling procedure required 5 h at room temperature for completion and 10 min at reflux. The yield was 92% after purification by column chromatography (petroleum ether/ethyl acetate, 20/1); ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.34 (m, 4 H, 2 CH_2), 1.62 (m, 2 H, CH_2), 2.46 (t, 2 H, J = 6.8 Hz, CH_2), 7.52 (d, 1 H, J_{ortho} = 8.6 Hz, C_6H_3), 8.05 (dd, 1 H, J_{ortho} = 8.6 Hz, J_{meta} = 2.3 Hz, C_6H_3), 8.42 (d, 1 H, J_{meta} = 2.3 Hz, C_6H_3); MS m/e (rel %) 297 (23.6) ($M^{\bullet+}$), 295 (24.8) ($M^{\bullet+}$), 282 (27.6) ($M^{\bullet+} - CH_3^{\bullet}$), 280 (40.7) ($M^{\bullet+} - CH_3^{\bullet}$), 251 (10) ($M^{\bullet+} - NO_2^+$), 249 (6.9) ($M^{\bullet+} - NO_2^+$), 216 (4.2) ($M^{\bullet+} - Br^{\bullet}$), 194 (19.7), 141 (23.5); HRMS m/e calcd for $C_{13}H_{14}NO_2{}^{79}Br$ 295.0208, found 295.0221.

***p*-*n*-Heptylaniline (3a).** A solution of 1-(2-bromo-4-nitrophenyl)heptyne (2) (3.39 mmol, 1 g) in 20 mL of ethanol containing 20 mg of 5% Pd/C was hydrogenated at slightly above atmospheric pressure until the uptake of hydrogen stopped. The reaction mixture was filtered, concentrated, and purified by column chromatography (petroleum ether/ethyl acetate, 2/1) to give **3a**[21] as a yellow oil in 75% yield: ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.27 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.45 (t, 2 H, J = 7.6 Hz, $CH_2(C_6H_4)$), 3.50 (br s, 2 H, NH_2), 6.60 (d, 2 H, J_{ortho} = 8.0 Hz, C_6H_4), 6.95 (d, 2 H, J_{ortho} = 8.0 Hz, C_6H_4); MS m/e (rel %) 191 (37.2) ($M^{\bullet+}$), 175 (10.0) ($M^{\bullet+} - NH_2^+$), 119 (13.8), 106 (100) ($M^{\bullet+} - (CH_2)_5CH_3^{\bullet}$); HRMS m/e calcd for $C_{13}H_{21}N$ 191.1674, found 191.1594.

***p*-*n*-Heptylacetanilide (3b).** *p*-*n*-Heptylaniline (3a) (2.6 mmol, 500 mg) in 5 mL of pyridine at 0 °C was treated with acetyl chloride (5.2 mmol, 0.37 mL). The reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure to give a residue. The residue was dissolved in diethyl ether (100 mL), and this was repeatedly washed with portions of 1% aqueous hydrochloric acid (4 × 10 mL). The combined extracts were dried over $MgSO_4$, concentrated, and purified by column chromatography (petroleum ether/ethyl acetate, 1/2) to give **3b** as an oil in quantitative yield: ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.27 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.15 (s, 3 H, $COCH_3$), 2.45 (t, 2 H, J = 7.6 Hz, $CH_2(C_6H_4)$), 6.60 (d, 2 H, J = 8.3 Hz, C_6H_4), 6.90 (d, 2 H, J = 8.3 Hz, C_6H_4), 7.71 (s, 1 H, NH); MS m/e (rel %) 233 (30.6) ($M^{\bullet+}$), 191 (20.7), 148 (27.6) ($M^{\bullet+} - (CH_2)_5CH_3^{\bullet}$), 134 (16.0) ($M^{\bullet+} - C_7H_{15}$); HRMS m/e calcd for $C_{15}H_{23}NO$ 233.1779, found 233.1802.

3-Nitro-1,2-dibromobenzene (4). After recrystallization from methanol, the mp was 84.5–85 °C (lit.[9] mp 85 °C). The yield was 16%: ^1H NMR δ 7.26 (dd, 1 H, J_{ortho} = 8.0 Hz, C_6H_3), 7.61 (dd, 1 H, J_{meta} = 1.3 Hz, J_{ortho} = 6.9 Hz, C_6H_3), 7.82 (dd, 1 H, J_{meta} = 1.3 Hz, J_{ortho} = 6.9 Hz, C_6H_3); MS m/e (rel %) a 1:2:1 triplet at 283 (10.2) ($M^{\bullet+}$), 281 (20.4) ($M^{\bullet+}$), 279 (10.2) ($M^{\bullet+}$), and 237 (22.2) ($M^{\bullet+}$), 235 (44.4) ($M^{\bullet+}$), 233 (22.3) ($M^{\bullet+}$); HRMS m/e calcd for $C_6H_3NO_2{}^{79}Br_2$ 278.8531, found 278.8535.

1-(2-Bromo-6-nitrophenyl)heptyne (5). The coupling of 3-nitro-1,2-dibromobenzene (4) with 1-heptyne using the general coupling procedure required 5 h at reflux temperature for completion. The yield was 82% after purification by column chromatography (petroleum ether/ethyl acetate, 20/1): ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.33 (m, 4 H, 2 CH_2), 1.59 (m, 2 H, CH_2), 2.41 (t, 2 H, J = 7.0 Hz, CH_2), 7.18 (d, 1 H, J_{ortho} = 8.2 Hz, C_6H_3), 7.56 (dd, 1 H, J_{meta} = 1.3 Hz, J_{ortho} = 8.0 Hz, C_6H_3), 7.81 (dd, 1 H, J_{meta} = 1.3 Hz, J_{ortho} = 8.0 Hz, C_6H_3); MS m/e (rel %) 297 (2.7) ($M^{\bullet+}$), 295 (2.9) ($M^{\bullet+}$), 282 (1.8) ($M^{\bullet+} - CH_3^{\bullet}$), 280 (2.1) ($M^{\bullet+} - CH_3^{\bullet}$), 251 (9.6) ($M^{\bullet+} - NO_2^+$), 249 (10.8) ($M^{\bullet+} - NO_2^+$), 197 (6.5), 170 (10.7), 129 (28.5); HRMS m/e calcd for $C_{13}H_{14}NO_2{}^{79}Br$ 295.0208, found 295.0240.

***o*-*n*-Heptylaniline (6a).** Reduction of 1-(2-bromo-6-nitrophenyl)heptyne (5) was done in the similar manner as reduction of 2 to produce aniline **3a**. The yield was 75% after purification by column chromatography (petroleum ether/ethyl acetate, 2/1): ^1H NMR δ 0.84 (t, 3 H, J = 7.0 Hz, CH_3), 1.27 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.45 (t, 2 H, J = 7.6 Hz, $CH_2(C_6H_4)$), 3.50 (br s, 2 H, C_6H_4), 6.99 (m, 2 H, C_6H_4); MS m/e (rel %) 191 (42.3) ($M^{\bullet+}$), 175 (20.2) ($M^{\bullet+} - NH_2^+$), 130 (15), 106 (100) ($M^{\bullet+} - (CH_2)_5CH_3^{\bullet}$); HRMS m/e calcd for $C_{13}H_{21}N$ 191.1673, found 191.1706.

***o*-*n*-Heptylacetanilide (6b).** Acetylation of **6a** to produce acetamido **6b** was done in the similar manner as described above for the acetylation of **3a** to **3b**. The yield was quantitative after column chromatography (petroleum ether/ethyl acetate, 1/2): ^1H NMR δ 0.84 (t, 3 H, J = 7.0 Hz, CH_3), 1.27 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.16 (s, 3 H, $COCH_3$), 2.49 (t, 2 H, J = 7.3 Hz, $CH_2(C_6H_4)$), 7.08 (m, 2 H, C_6H_4), 7.20 (m, 2 H, C_6H_4), 7.64 (s, 1 H, NH); MS m/e (rel %) 233 (35.2) ($M^{\bullet+}$), 218 (5.3) ($M^{\bullet+} - CH_3^{\bullet}$), 191 (26.9), 190 (47.2) ($M^{\bullet+} - (CH_2)_2CH_3^{\bullet}$), or ($M^{\bullet+} - COCH_3^{\bullet}$), 162 (30.9); HRMS m/e calcd for $C_{15}H_{23}NO$ 233.1779, found 233.1735.

4-Amino-1,2-dibromobenzene (7a).[22] To a solution of 4-nitro-1,2-dibromobenzene (1) (10.8 mmol, 3 g) in NEt_3 (15 mL) at 0 °C under 1 atm of nitrogen was added 98% formic acid (35.7

(21) Compound **3a** has the same ^1H NMR and mass spectrometry data as reported by Ito, K.; Komori, A.; Ogawa, M. *Technol. Rept. Kansai Univ. No. 5* **1963**, 31.

(22) The procedure used for the reduction was developed by: Heck, R. F.; Cortese, N. A. *J. Org. Chem.* **1977**, *42*, 3491. To prevent debromination the catalyst used was $Pt(IV)O_2$.

mmol, 1.35 mL) and $Pt(IV)O_2$ (0.53 mmol, 120 mg). The reaction mixture was warmed to room temperature, poured into methylene chloride (500 mL), and washed with saturated solution of NH_4Cl (2 × 30 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (petroleum ether/ethyl acetate, 2/1) to give **7a**, mp 78–79 °C (lit.[23] mp 81 °C), in 92% yield: ^1H NMR[24] δ 3.69 (br s, 2 H, NH_2), 6.44 (dd, 1 H, J_{meta} = 2.7 Hz, J_{ortho} = 6.0 Hz, C_6H_3), 6.93 (d, 1 H, J_{meta} = 2.7 Hz, C_6H_3), 7.28 (d, 1 H, J_{ortho} = 8.6 Hz, C_6H_3); MS *m/e* (rel %) a 1:2:1 triplet at 253 (19.6) ($M^{\bullet+}$), 251 (22.7) ($M^{\bullet+}$), 249 (21.1) ($M^{\bullet+}$), and 172 (51.3) ($M^{\bullet+}$ – $Br^{\bullet}$), 170 (43.1) ($M^{\bullet+}$ – $Br^{\bullet}$), 145 (18.7), 143 (18.8); HRMS *m/e* calcd for $C_6H_5N^{79}Br_2$ 248.8789, found 248.8829.

4-Acetamido-1,2-dibromobenzene (7b). Acetylation of **7a** to produce acetamido **7b** was done in the similar manner as described above for the acetylation of **3a** to **3b**. The yield was quantitative after column chromatography (petroleum ether/ethyl acetate, 1/2): ^1H NMR δ 7.08 (dd, 1 H, J_{meta} = 2.4 Hz, J_{ortho} = 6.6 Hz, C_6H_3), 7.32 (d, 1 H, J_{meta} = 2.5 Hz, C_6H_3), 7.44 (d, 1 H, J_{ortho} = 8.0 Hz, C_6H_3); MS *m/e* (rel %) a 1:2:1 triplet at 295 (20) ($M^{\bullet+}$), 293 (42.3) ($M^{\bullet+}$), 291 (20) ($M^{\bullet+}$), and 252 (3.1) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 250 (9.3) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 248 (3.1) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 191 (9.3); HRMS *m/e* calcd for $C_8H_7NO^{79}Br_2$ 290.8895, found 290.8890.

1-(2-Bromo-5-aminophenyl)heptyne (8a). The coupling of 4-amino-1,2-dibromobenzene (**7a**) with 1-heptyne using the general coupling procedure required 38 h at reflux temperature for completion. The yield was 70% after purification by column chromatography (petroleum ether/ethyl acetate, 2/1): ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.33 (m, 4 H, 2 CH_2), 1.59 (m, 2 H, CH_2), 2.41 (t, 2 H, J = 7.0 Hz, CH_2), 3.50 (br s, 2 H, NH_2), 6.43 (dd, 1 H, J_{meta} = 2.8 Hz, J_{ortho} = 5.7 Hz, C_6H_3), 6.75 (d, 1 H, J_{meta} = 2.8 Hz, C_6H_3), 7.25 (d, 1 H, J_{ortho} = 8.6 Hz, C_6H_3); MS *m/e* (rel %) 267 (81.6) ($M^{\bullet+}$), 265 (66.6) ($M^{\bullet+}$), 210 (53.0) ($M^{\bullet+}$ – $(CH_2)_3CH_3^{\bullet}$), 208 (51.7) ($M^{\bullet+}$ – $(CH_2)_3CH_3^{\bullet}$), 186 (6.3) ($M^{\bullet+}$ – $Br^{\bullet}$), 158 (61.4), 156 (31.9); HRMS *m/e* calcd for $C_{13}H_{16}N^{79}Br$ 265.0466, found 265.0520.

1-(2-Bromo-5-acetamidophenyl)heptyne (8b). Acetamido **8b** was produced from the coupling reaction of 4-acetamido-1,2-dibromobenzene (**7b**) with 1-heptyne using the general coupling procedure which required 6 h at reflux for completion. The yield was 78% after purification by column chromatography (petroleum ether/ethyl acetate, 2/1): ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.33 (m, 4 H, 2 CH_2), 1.59 (m, 2 H, CH_2), 2.16 (s, 3 H, $COCH_3$), 2.40 (t, 3 H, J = 7.0 Hz, CH_2), 7.08 (br s, 1 H, NH), 7.15 (dd, 1 H, J_{meta} = 2.4 Hz, J_{ortho} = 6.6 Hz, C_6H_3), 7.25 (d, 1 H, J_{meta} = 2.5 Hz, C_6H_3), 7.44 (d, 1 H, J_{ortho} = 8.0 Hz, C_6H_3); MS *m/e* (reg %) 309 (6.8) ($M^{\bullet+}$), 307 (7.0) ($M^{\bullet+}$), 280 (14.6) ($M^{\bullet+}$ – $CH_2CH_3^{\bullet}$), 278 (14.8) ($M^{\bullet+}$ – $CH_2CH_3^{\bullet}$), 266 (4.9) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 264 (2.6) ($M^{\bullet+}$ – $COCH_3^{\bullet}$); HRMS *m/e* calcd for $C_{15}H_{18}NO^{79}Br$ 307.0571, found 307.0571.

Identical ^1H NMR and MS data were obtained when 1-(2-bromo-5-aminophenyl)heptyne (**8a**) was treated under acetylation conditions as described for the transformation of **3a** to acetamido **3b**. The yield was quantitative after purification by column chromatography (petroleum ether/ethyl acetate, 1/2).

***m*-*n*-Heptylaniline (9a).** Catalytic hydrogenation as described for the transformation of **2** to **3a** was employed for the reduction of **8a** and **11a**. Both reductions after purification by column chromatography (petroleum ether/ethyl acetate, 2/1) gave **9a** in 75% yield: ^1H NMR δ 0.83 (t, 3 H, J = 7.0 Hz, CH_3), 1.27 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.45 (t, 2 H, J = 7.6 Hz, CH_2-(C_6H_4)), 3.50 (br s, 2 H, NH_2), 6.55 (m, 3 H, C_6H_4), 7.02 (m, 1 H, C_6H_4); MS *m/e* (rel %) 191 (36.7) ($M^{\bullet+}$), 148 (2.0) ($M^{\bullet+}$ – $(CH_2)_2CH_3^{\bullet}$), 107 (100); HRMS *m/e* calcd for $C_{13}H_{21}N$ 191.1673, found 191.1639.

***m*-*n*-Heptylacetanilide (9b).** Catalytic hydrogenation as described for the transformation of **2** to **3** was employed for the reduction of **8b** and **11b**. Both reductions after purification by column chromatography (petroleum ether/ethyl acetate, 1/2) gave **9b** in 75% yield. Acetylation of **9a** had also given **9b** in quantitative yield: ^1H NMR δ 0.83 (t, 3 H, J = 7.0 Hz, CH_3), 1.22 (m, 8 H, 4 CH_2), 1.51 (m, 2 H, CH_2), 2.15 (s, 3 H, $COCH_3$), 2.51 (t, 3 H, J = 7.0 Hz, CH_2), 7.08 (br s, 1 H, NH), 7.12 (m, 2 H, C_6H_4), 7.25 (m, 2 H, C_6H_4); MS *m/e* (rel %) 233 (5.5) ($M^{\bullet+}$), 218 (10.0) ($M^{\bullet+}$ – $CH_3^{\bullet}$), 190 (5.3) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 149 (10.5); HRMS *m/e* calcd for $C_{15}H_{23}NO$ 233.1779, found 233.1807.

3-Amino-1,2-dibromobenzene (10a). Using the procedure for the transformation of **1** to **7a**, 3-nitro-1,2-dibromobenzene (**4**) was converted to **10a**, mp 44–45 °C (lit.[23] mp 43 °C), in 92% yield: ^1H NMR[24] δ 3.97 (br s, 2 H, NH_2), 6.66 (dd, 1 H, J = 2.0 Hz, J = 5.5 Hz, C_6H_3), 6.92 (m, 2 H, C_6H_3), 6.92 (m, 2 H, C_6H_3); MS *m/e* (rel %) a 1:2:1 triplet at 253 (68.6) ($M^{\bullet+}$), 251 (100) ($M^{\bullet+}$), 249 (75.3) ($M^{\bullet+}$), and 172 (19.9) ($M^{\bullet+}$ – $Br^{\bullet}$), 170 (30.6) ($M^{\bullet+}$ – $Br^{\bullet}$), 145 (6.4), 143 (7.8); HRMS *m/e* calcd for $C_6H_5{}^{79}Br_2N$ 248.8847, found 248.8847.

1,2-Dibromo-3-acetamidobenzene (10b). Acetylation of **10a** to produce acetamido **10b** was done in the similar manner as described above for the acetylation of **3a** to **3b**. The yield was quantitative after column chromatography (petroleum ether/ethyl acetate, 1/2): ^1H NMR δ 2.15 (s, 3 H, $COCH_3$), 6.88 (br s, 1 H, NH), 6.93 (m, 1 H, C_6H_3), 6.98 (m, 2 H, C_6H_3); MS *m/e* (rel %) a 1:2:1 triplet at 295 (30) ($M^{\bullet+}$), 293 (60) ($M^{\bullet+}$), 291 (33) ($M^{\bullet+}$), and 252 (48) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 250 (6.3) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 248 (2.1) ($M^{\bullet+}$ – $COCH_3^{\bullet}$); HRMS *m/e* calcd for $C_8H_7NO^{79}Br_2$ 290.8895, found 290.8890.

1-(2-Bromo-3-aminophenyl)heptyne (11a). The coupling of 3-amino-1,2-dibromobenzene (**10a**) with 1-heptyne using the general coupling procedure required 3 days at reflux temperature for completion. The yield was 72% after purification by column chromatography (petroleum ether/ethyl acetate, 2/1): ^1H NMR δ 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.30 (m, 4 H, 2 CH_2), 1.51 (m, 2 H, CH_2), 2.41 (t, 2 H, J = 6.8 Hz, CH_2), 4.15 (br s, 2 H, NH_2), 6.64 (dd, 1 H, J_{ortho} = 7.9 Hz, J_{meta} = 1.6 Hz, C_6H_3), 6.82 (dd, 1 H, J_{ortho} = 7.9 Hz, J_{meta} = 1.6 Hz, C_6H_3), 6.91 (d, J_{ortho} = 7.8 Hz, C_6H_3); MS *m/e* (rel %) 267 (55.2) ($M^{\bullet+}$), 265 (32.3) ($M^{\bullet+}$), 210 (52.6) ($M^{\bullet+}$ – $(CH_2)_3CH_3^{\bullet}$), 186 (10.3) ($M^{\bullet+}$ – $Br^{\bullet}$); HRMS *m/e* calcd for $C_{13}H_{16}N^{79}Br$ 265.0466, found 265.0499.

1-(2-Bromo-3-acetamidophenyl)heptyne (11b). The coupling of 1,2-dibromo-3-acetamidobenzene **10b** with 1-heptyne using the general coupling procedure required 18 h at reflux temperature for completion. The yield was 76% after purification by column chromatography (petroleum ether/ethyl acetate, 1/2): ^1H NMR δ 0.83 (t, 3 H, J = 7.0 Hz, CH_3), 1.22 (m, 4 H, 2 CH_2), 1.52 (m, 2 H, CH_2), 2.15 (s, 3 H, $COCH_3$), 2.51 (t, 3 H, J = 7.0 Hz, CH_2), 6.82 (br s, 1 H, NH), 6.88 (m, 2 H, C_6H_3), 6.91 (m, 1 H, C_6H_3); MS *m/e* (rel %) 309 (18.2) ($M^{\bullet+}$), 307 (20.1) ($M^{\bullet+}$), 280 (2.3) ($M^{\bullet+}$ – $CH_2CH_3^{\bullet}$), 278 (2.5) ($M^{\bullet+}$ – $CH_2CH_3^{\bullet}$), 266 (7.3) ($M^{\bullet+}$ – $COCH_3^{\bullet}$), 264 (7.8) ($M^{\bullet+}$ – $COCH_3^{\bullet}$); HRMS *m/e* calcd for $C_{15}H_{18}ON^{79}Br$ 307.0571, found 307.0571.

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Supplementary Material Available: ^1H NMR spectra for the compounds produced in this study (26 pages). Ordering information is given on any current masthead page.

(23) *Handbook of Chemistry and Physics*, 55th ed.; The Chemical Rubber Co.: Cleveland, 1974–1975; p c-108.

(24) Compounds **7a** and **10a** have same ^1H NMR and MS data as that reported by: Liedholm, B. *Acta Chem. Scand., Ser. B* **1984**, *B38*(10), 877.