H), 4.7 (s, 1 H), 6.6-7.5 (q, 4 H).

4-Me-MOAAN: mp 89-90.5 °C (lit.[25] bp 120-122 °C (4 Torr)); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.5-2.6 (m, 4 H), 3.6-3.8 (m, 4 H), 4.73 (s, 1 H), 7.15-7.5 (m, 4 H).

3-Me-MOAAN: mp 59.5-61 °C (lit.[27] mp 59-60 °C); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.5 (m, 4 H), 3.6 (m, 4 H), 4.7 (s, 1 H), 7.1-7.3 (m, 4 H).

4-F-MOAAN: mp 64.5-66.0 °C (lit.[27] mp 60-63 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.75 (s, 1 H), 6.9-7.7 (m, 4 H).

3,4-(methylenedioxy)-MOAAN: mp 117.0-117.5 °C (lit.[28] mp 118-120 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.3-3.5 (m, 4 H), 4.68 (s, 1 H), 5.98 (s, 2 H), 6.7-7.3 (m, 3 H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.31; H, 5.61.

MOAAN: mp 67-69 °C (lit.[22] mp 68-70 °C); ^{1}H NMR ($CDCl_3$) δ 2.5-2.7 (m, 4 H), 3.65-3.8 (m, 4 H), 4.8 (s, 1 H), 7.4-7.7 (m, 5 H).

3-MeO-MOAAN: mp 44.5-45.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.4-3.9 (m, 4 H), 3.8 (s, 3 H), 4.7 (s, 1 H), 6.8-7.5 (m, 4 H). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.02; H, 6.87.

4-Cl-MOAAN: mp 75-76 °C (lit.[27] mp 70-71 °C).

3-Cl-MOAAN: mp 71.5-72.5 °C (lit.[25] mp 72-73 °C).

3-CN-MOAAN: mp 101.0-101.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.8 (s, 1 H), 7.3-7.9 (m, 4 H). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77. Found: C, 68.19; H, 5.57.

3,4-Cl_2-MOAAN: mp 74.3-74.9 °C (lit.[27] mp 62-64 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.55-3.75 (m, 4 H), 4.7 (s, 1 H), 7.1-7.6 (m, 3 H). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 53.16; H, 4.46. Found: C, 53.52; H, 4.41.

4-CF_3-MOAAN: mp 89-90 °C (lit.[27] mp 89-90 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.75 (s, 1 H), 7.65 (s, 4 H).

4-CN-MOAAN: mp 117-118 °C (lit.[26] mp 128-128.5 °C).

Acknowledgment. This research was supported by a grant from the National Science Foundation.

Registry No. 4-(Me_2N)-MOAAN, 17766-45-9; 4-(Me_2N)-MOAAN (anion), 123567-65-7; 4-MeO-MOAAN, 15190-13-3; 4-MeO-MOAAN (anion), 123567-66-8; 4-Me-MOAAN, 42419-53-4; 4-Me-MOAAN (anion), 123567-68-0; 3,4-(-OCH_2O-)-MOAAN, 37673-10-2; 3,4-(-OCH_2O-)-MOAAN (anion), 123567-70-4; 3-Me-MOAAN, 66549-30-2; 3-Me-MOAAN (anion), 123567-69-1; 4-F-MOAAN, 68415-10-1; 4-F-MOAAN (anion), 123567-86-2; MOAAN, 15190-10-0; MOAAN (anion), 123567-64-6; 3-MeO-MOAAN, 123567-57-7; 3-MeO-MOAAN (anion), 123567-67-9; 4-Cl-MOAAN, 33599-26-7; 4-Cl-MOAAN (anion), 123567-88-4; 3-Cl-MOAAN, 66548-90-1; 3-Cl-MOAAN (anion), 123567-87-3; 3-CN-MOAAN, 123567-58-8; 3-CN-MOAAN (anion), 123567-92-0; 3,4-Cl_2-MOAAN, 66549-47-1; 3,4-Cl_2-MOAAN (anion), 123567-89-5; 4-CF_3-MOAAN, 66573-60-2; 4-CF_3-MOAAN (anion), 123567-90-8; 4-CN-MOAAN, 28951-73-7; 4-CN-MOAAN (anion), 123567-91-9; 4-(Me_2N)-PAAN, 123567-59-9; 4-(Me_2N)-PAAN (anion), 123567-72-6; 4-MeO-PAAN, 15190-14-4; 4-MeO-PAAN (anion), 123567-73-7; 4-Me-PAAN, 42419-52-3; 4-Me-PAAN (anion), 123567-74-8; PAAN, 5766-79-0; PAAN (anion), 123567-71-5; 4-Cl-PAAN, 64661-38-7; 4-Cl-PAAN (anion), 123567-75-9; 3-Cl-PAAN, 42419-54-5; 3-Cl-PAAN (anion), 123567-76-0; 3,4-Cl_2-PAAN, 123567-60-2; 3,4-Cl_2-PAAN (anion), 123567-77-1; 4-Me-CAAN, 81311-83-3; 4-Me-CAAN (anion), 123567-80-6; 3-Me-CAAN, 123567-61-3; 3-Me-CAAN (anion), 123567-79-3; CAAN, 3893-23-0; CAAN (anion), 123567-78-2; 4-Cl-CAAN, 76618-95-6; 4-Cl-CAAN (anion), 123567-81-7; 3-Cl-CAAN, 85522-98-1; 3-Cl-CAAN (anion), 123567-82-8; 3-CF_3-CAAN, 123567-62-4; 3,4-Cl_2-CAAN, 123567-63-5; 3,4-Cl_2-CAAN (anion), 123567-83-9; PhCOMe, 98-86-2; PhCOMe (anion), 34438-71-6; $PhCOCH_2Ph$, 451-40-1; $PhCOCH_2Ph$ (anion), 54282-53-0; c-$C_5H_{10}NCH_2COPh$, 779-52-2; c-$C_5H_{10}NCH_2COPh$ (anion), 123567-84-0; c-$C_5H_{10}NCH(Ph)COPh$, 794-05-8; c-$C_5H_{10}NCH(Ph)COPh$ (anion), 123567-85-1; $PhCOCHPh_2$, 1733-63-7; $PhCOCHPh_2$ (anion), 111286-46-5; $PhCH_2CN$, 140-29-4; $PhCH_2CN$ (anion), 18802-89-6; Ph_2CHCN, 86-29-3; Ph_2CHCN (anion), 18802-83-0; CH_4, 74-82-8; PhMe, 108-88-3; Ph_2CH_2, 101-81-5; Ph_3CH, 519-73-3; Ph_2CH_2 (anion), 18802-87-4; Ph_3CH (anion), 40006-86-8; p-$MeC_6H_4CH_2CN$, 2947-61-7; m-$MeC_6H_4CH_2CN$, 2947-60-6; m-$ClC_6H_4CH_2CN$, 1529-41-5; m-$CF_3C_6H_4CH_2CN$, 2338-76-3; p-$Me_2NC_6H_4CHO$, 100-10-7; p-MeC_6H_4CHO, 104-87-0; 3,4-(-OCH_2O-)C_6H_3CHO, 120-57-0; m-MeC_6H_4CHO, 620-23-5; p-FC_6H_4CHO, 459-57-4; PhCHO, 100-52-7; m-$MeOC_6H_4CHO$, 591-31-1; p-ClC_6H_4CHO, 104-88-1; m-ClC_6H_4CHO, 587-04-2; m-CNC_6H_4CHO, 24964-64-5; 3,4-$Cl_2C_6H_3CHO$, 6287-38-3; p-$CF_3C_6H_4CHO$, 455-19-6; p-CNC_6H_4CHO, 105-07-7; p-$MeOC_6H_4CHO$, 123-11-5; c-$C_6H_{11}Br$, 108-85-0; c-$C_5H_{10}N$, 110-89-4; morpholine, 110-91-8.

(27) Albright, J. D.; McEvoy, F. G.; Moran, D. B. *J. Heterocycl. Chem.* **1978**, *15*, 881-892.
(28) McEvoy, F. J.; Albright, L. D. *J. Org. Chem.* **1979**, *44*, 4597-4603.

Palladium-Catalyzed Alkenylation and Alkynylation of Polyhaloarenes

Weijin Tao, Stephanie Nesbitt, and Richard F. Heck*

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

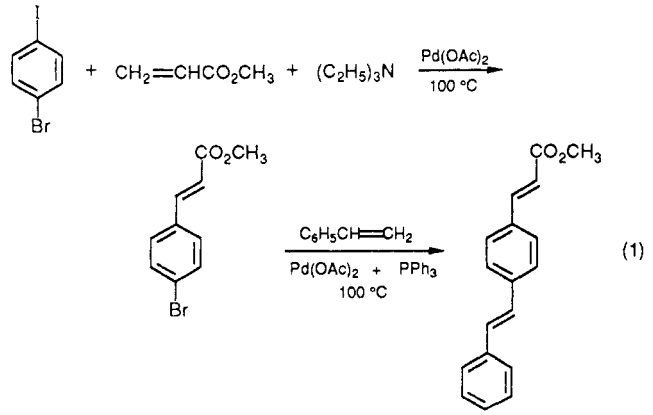
Received June 21, 1989

Alkenylation of several polyhaloarenes proceeded in low to moderate yields. Iodo groups could be reacted selectively in the presence of bromo groups; however, no more than two alkenyl groups could be introduced on contiguous, aromatic carbons. Alkynylation was more successful. Even hexa- and pentaalkynylarenes were obtainable in reasonable yields. Again, iodo groups could be reacted selectively in the presence of bromo groups. Convenient syntheses of a variety of 1,2,4,5-, 1,3,4,5-, and 1,2,4,6-tetrasubstituted aromatic compounds are possible by use of these reactions.

Several years ago we reported the palladium-catalyzed dialkenylation of *o*- and *p*-diiodobenzene[1] and later the selective monoalkenylation of *o*- and *p*-bromoiodobenzenes.[2] In the last examples it was noted that only the iodo group reacted when palladium acetate was the catalyst while both iodo and bromo groups reacted if a triarylphosphine was present in addition to the palladium acetate.[2] Chloro substituents were unreactive with either catalyst system.[3] Little additional work has been reported

(1) Plevyak, J. E.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2454.
(2) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.
(3) Cortese, N.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3907.

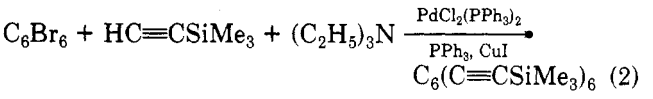
0022-3263/90/1955-0063$02.50/0



(1)

on the alkenylation of dihaloalkenes, and apparently trihalogenated and more highly halogenated arenes have not been studied at all. No doubt one reason for this lack of study has been the synthetic difficulties in obtaining polyhalogenated compounds, particularly polyiodides. In 1984, Mattern[4] reported a convenient, new procedure for the direct polyiodination of some arenes which does not appear to have been employed to prepare polyiodides for use in the palladium-catalyzed alkenylation. We thought these reactions were worth investigating because it seemed probable that a variety of highly substituted arenes could be easily prepared by their use.

Several other palladium-catalyzed reactions of aryl halides probably also could be applied to the polyhaloarenes, and substituents other than alkenyl groups likely could be introduced. One of these reactions in fact has been reported by Vollhardt,[5] the hexaalkynylation of hexabromobenzene. Both (trimethylsilyl)acetylene and 2-methyl-2-butyn-2-ol gave hexaalkynylbenzenes in good yields.

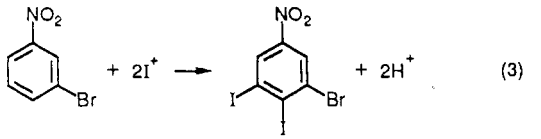


(2)

We report herein further examples of the polyalkynylation and polyalkenylation which demonstrate the value of polyhalides in preparing highly substituted aromatic compounds.

Results and Discussion

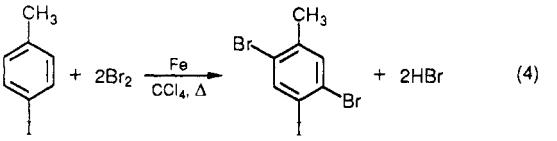
Polyhalides. Several polyiodides were prepared by the method of Mattern.[4] The reported products,[4] hexaiodobenzene, 1,2,4,5-tetraiodobenzene, pentaiodotoluene, 2,4,5-triiodotoluene, pentaiodobenzoic acid, 3,4,5-triiodobenzoic acid, and 3,4,5-triiodonitrobenzene, were all prepared by the periodic acid–iodine–sulfuric acid iodination of the parent compounds by the general method described. It is interesting and of synthetic value that toluene yields the 2,4,5-triiodo derivative, while with an electron-withdrawing substituent as in benzoic acid or nitrobenzene, the 3,4,5-triiodo products are formed. We extended the reaction to the *o*-, *m*-, and *p*-bromotoluenes and to *m*- and *p*-bromonitrobenzenes. With 10 equiv of "I^+" the 2,4,5-trihalides were the only products isolated from the bromotoluenes, and only the 3,4,5-trihalides were obtained from the bromonitrobenzenes. The structures of the trihalides were based upon ^1H NMR spectra. Aryl protons in the trihalotoluenes ($CDCl_3$) between two iodo groups appear at 8.2 ± 0.1 ppm, between an iodo and bromo group



(3)

at 7.9 ± 0.1, between iodo and methyl at 7.7 ± 0.1, between bromo and methyl at 7.9 ± 0.1, and in the trihalonitrobenzenes ($CDCl_3$) between nitro and iodo at 8.6 ± 0.1 and between nitro and bromo at 8.4 ± 0.1 ppm.

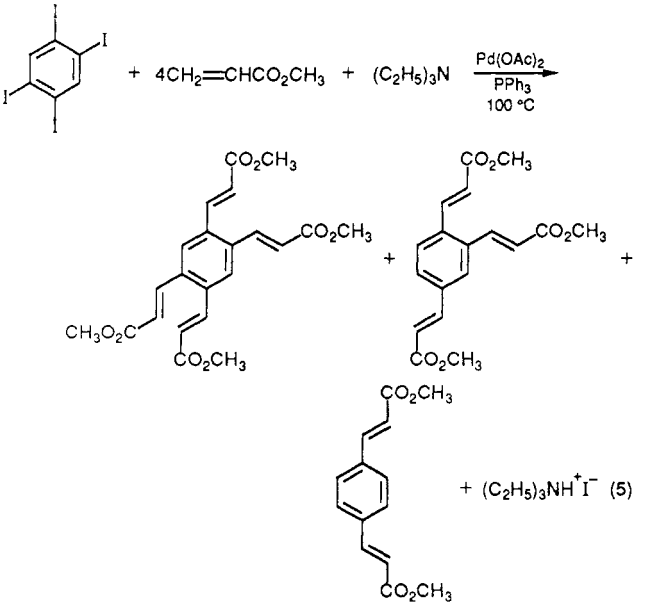
Also prepared was 2,5-dibromo-4-iodotoluene. This compound was obtained in 48% yield by the dibromination of *p*-iodotoluene.



(4)

Alkenylations. Hexaiodobenzene failed to form the hexaacrylyl derivative with excess methyl acrylate and a palladium acetate–triphenylphosphine catalyst at 100 °C. Instead only small amounts of the 1,2,4,5-tetraester (6%), the 1,2,4-triester (4%), and the 1,4-diester (2%) were found. The major product was polymeric red oil. Likewise, pentaiodonitrobenzene did not give the pentaalkenyl derivative in reactions with styrene or *p*-methylstyrene. In this case no reaction at all occurred at 100 °C. We also reacted pentaiodotoluene with methyl acrylate at 100 °C, but again only products arising from partially reduced polyhalide were found in low yields. Therefore, it appears that hexasubstituted aryl iodides will not undergo simple alkenylation under the usual conditions but rather either do not react at all or undergo partial reduction of the iodo groups and give low yields of alkenylation products of the reduced iodides.

Several tetrasubstituted aryl iodides did undergo the normal alkenylation with methyl acrylate. 1,2,4,5-Tetraiodobenzene, in the reaction, gave 1,2,4,5-tetrakis[(methoxycarbonyl)ethenyl]benzene but only in 16% yield along with 9% of the 1,2,4-triester and 5% of the 1,4-diester.



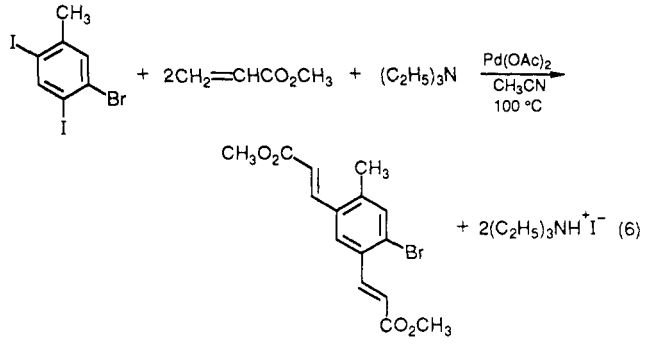
(5)

The structure of the diester was established by comparison of the product with those obtained from 1,2- and 1,4-diiodobenzenes. These and other results are summarized in Table I.

(4) Mattern, D. L. *J. Org. Chem.* **1984**, *49*, 3051.
(5) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 268.

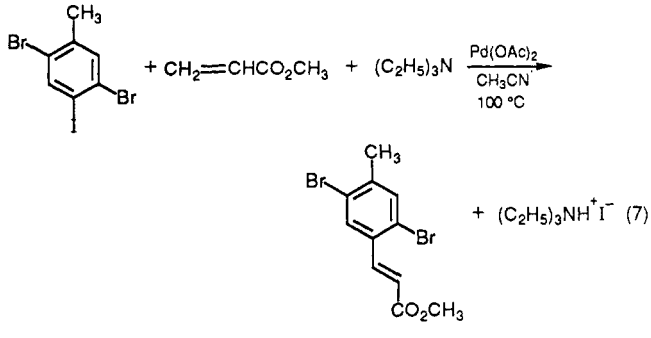
2,4,5-Triiodotoluene and methyl acrylate yield 52% of the expected triester along with only 2% of a diester. 3,4,5-Triiodonitrobenzene, however, did not give any of the possible esters but only 50% recovered triiodide and polymeric material. Styrene behaved similarly with the tri- and pentaiodonitrobenzene.

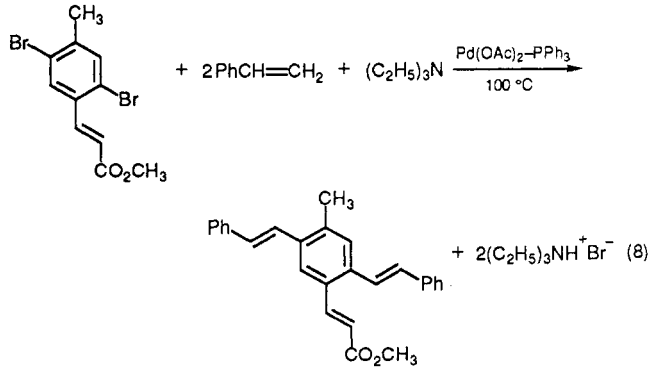
The bromodiodotoluenes can be selectively reaced at the iodo groups as we reported previously with dihalobenzenes.[2] Thus, 5-bromo-2,4-diiodotoluene, prepared by the diiodination of *m*-bromotoluene, and methyl acrylate with palladium acetate as catalyst gave 46% of the 1,3-diester.



The isomeric 2-bromo-4,5-diiodotoluene reacted with styrene, but one iodo group was lost in the reaction and only a mixture of 3-bromo-4-methyl- and 4-bromo-3-methylstilbenes was obtained (total yield 20%).

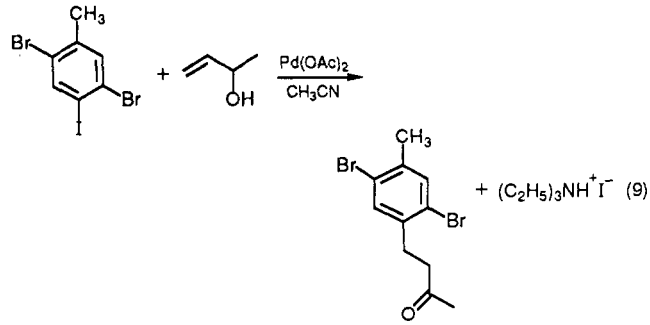
2,5-Dibromo-4-iodotoluene also reacted selectively at the iodo position with methyl acrylate (81%). The remaining bromo groups were still reactive and were both replaced in the palladium acetate–triphenylphosphine catalyzed reaction with styrene in 46% yield.

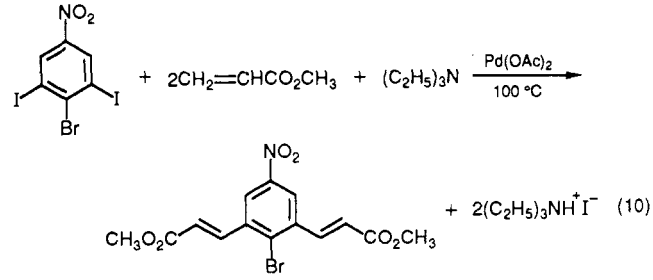




The bromodiiodide also reacted with 3-buten-2-ol to form the 4-(3-oxobutyl) derivative (71%).

Alkenylation of the 3,4,5-trihalonitrobenzenes is more difficult. The triiodide with methyl acrylate or styrene gave only recovered triiodide and intractable red, viscous oils under our usual reaction conditions. 3,5-Diiodo-4-bromonitrobenzene did, however, yield the 3,5-di-

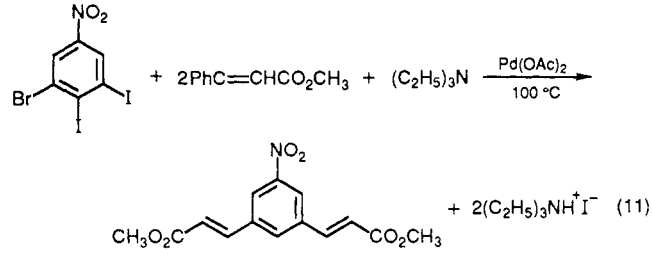




alkenylated product with methyl acrylate in 34% yield.

An attempt to replace all three halogens with acrylate groups with a palladium acetate–triphenylphosphine catalyst, however, was unsuccessful. Only the same bromo diester could be isolated from the reaction mixture in 16% yield.

3-Bromo-4,5-diiodonitrobenzene only formed a bisacrylyl derivative with methyl acrylate with loss of the 4-iodo group with a palladium acetate catalyst and that only occurred in 10% yield. No other significant pure product could be separated from the reaction mixture.



It may be concluded that three adjacent alkene substituents cannot be introduced into an aromatic ring by the palladium-catalyzed alkenylation reaction, at least under the conditions we employed. It appears that in the case of the 1,2,3-trihalides with two adjacent iodo groups that reduction of the central group is more facile than alkenylation. Competing reduction of iodo substituents in the hexaiodobenzene reaction also occurs so that no 1,2,3-trialkenyl derivatives are formed. The 4- or 5-iodo group was even lost from 2,4,5-triodotoluene when it was reacted with the less reactive alkene, styrene as compared with the methyl acrylate reaction, where all three iodo groups were replaced by the alkenyl groups.

Alkynylations. The report of Vollhardt[5] that hexabromobenzene could be hexaethynylated with (trimethylsilyl)acetylene employing a bis(triphenylphosphin)dichloropalladium–cuprous iodide catalyst suggested that alkynylation might occur more successfully than alkenylation did with our polyhalides. On the negative side, however, Vollhardt reported that hexaiodobenzene did not give significant yields of hexaethnylated products in the two cases he tried.[5]

Hexaiodobenzene was found to undergo hexaalkynylation with phenylacetylene in 53% yield in 14 h

Table I. Palladium-Catalyzed Reactions of Polyhaloarenes

haloarene	reactant	conditions	product (% yield)
I_6C_6	$CH_3O_2CCH{=}CH_2$	100 °C, 48 h	1,2,4,5-$(CH_3O_2CCH{=}CH)_4C_6H_2$ (6) 1,2,4-$(CH_3O_2CCH{=}CH)_3C_6H_3$ (4) 1,4-$(CH_3O_2CCH{=}CH)_2C_6H_4$ (2)
I_6C_6	$C_6H_5C{\equiv}CH$	50 °C, 14 h	1,2,3,4,5,6-$(C_6H_5C{\equiv}C)_6C_6$ (53)
1,2,4,5-$I_4C_6H_2$	$CH_3O_2CCH{=}CH_2$	100 °C, 48 h	1,2,4,5-$(CH_3O_2CCH{=}CH)_4C_6H_2$ (16) 1,2,4-$(CH_3O_2CCH{=}CH)_3C_6H_3$ (9) 1,4-$(CH_3O_2CCH{=}CH)_2C_6H_4$ (5)
1,2,4,5-$I_4C_6H_2$	$C_6H_5C{\equiv}CH$	25 °C, 12 h	1,2,4,5-$(C_6H_5C{\equiv}C)_4C_6H_2$ (63)
1,4-$I_2C_6H_4$	$CH_3O_2CCH{=}CH_2$	100 °C, 48 h	1,4-$(CH_3O_2CCH{=}CH)_2C_6H_4$ (32)
1,2-$I_2C_6H_4$	$CH_3O_2CCH{=}CH_2$	100 °C, 48 h	1,2-$(CH_3O_2CCH{=}CH)_2C_6H_4$ (69)
HO-2,4,6-$I_3C_6H_2$	$C_6H_5C{\equiv}CH$	50 °C, 12 h	HO-2,4,6-$(C_6H_5C{\equiv}C)_3C_6H_2$ (62)
$CH_3I_5C_6$	$C_6H_5C{\equiv}CH$	50 °C, 12 h	CH_3-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$ (51)
CH_3-2,4,5-$I_3C_6H_2$	$CH_3O_2CCH{=}CH_2$	100 °C, 12 h	CH_3-2,4,5-$(CH_3O_2CCH{=}CH)_3C_6H_2$ (52) $CH_3(CH_3O_2CCH{=}CH)_2C_6H_3$ (2)
CH_3-2,4,5-$I_3C_6H_2$	$C_6H_5C{\equiv}CH$	25 °C, 3 h	CH_3-2,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$ (87)
CH_3-2-Br-4,5-$I_2C_6H_2$	$C_6H_5CH{=}CH_2$	100 °C, 18 h	3-Br-4-$CH_3C_6H_3CH{=}CHC_6H_5$ 4-Br-3-$CH_3C_6H_3CH{=}CHC_6H_5$ (20)
CH_3-5-Br-2,4-$I_2C_6H_2$	$CH_3O_2CCH{=}CH_2$	100 °C, 19 h	1,3-$(CH_3O_2CCH{=}CH)_2$-4-Br-6-$CH_3C_6H_2$ (46)
CH_3-4-Br-2,5-$I_2C_6H_2$	$C_6H_5C{\equiv}CH$	25 °C, 2 h	1,4-$(C_6H_5C{\equiv}C)_2$-5-Br-2-$CH_3C_6H_2$ (84)
CH_3-2,5-Br_2-4-IC_6H_2	$CH_3O_2CCH{=}CH_2$	100 °C, 16.5 h	$(CH_3O_2CCH{=}CH)$-2,5-Br_2-4-$CH_3C_6H_2$ (81)
CH_3-2,5-Br_2-4-IC_6H_2	$CH_2{=}CHCH(OH)CH_3$	100 °C, 18 h	$(CH_3COCH_2CH_2)$-2,5-Br_2-4-$CH_3C_6H_2$ (71)
$(CH_3O_2CCH{=}CH)$-2,5-Br_2-4-$CH_3C_6H_2$	$C_6H_5CH{=}CH_2$	100 °C, 22 h	$(CH_3O_2CCH{=}CH)$-2,5-$(C_6H_5CH{=}CH)_2$-4-$CH_3C_6H_2$ (46)
HO_2C-2,3,4,5,6-I_5C_6	$C_6H_5C{\equiv}CH$	50 °C, 12 h	HO_2C-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$ (32)
HO_2C-3,4,5-$I_3C_6H_2$	$C_6H_5C{\equiv}CH$	50 °C, 12 h	HO_2C-3,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$ (53)
NO_2-3,4,5-$I_3C_6H_2$	$C_6H_5C{\equiv}CH$	50 °C, 12 h	1,2,3-$(C_6H_5C{\equiv}C)_3$-5-$NO_2C_6H_2$ (50)
NO_2-3,4,5-$I_3C_6H_2$	$(CH_3)_3SiC{\equiv}CH$	50 °C, 12 h	1,2,3-$((CH_3)_3SiC{\equiv}C)_3$-5-$NO_2C_6H_2$ (3)
NO_2-4-Br-3,5-$I_2C_6H_2$	$CH_3O_2CCH{=}CH_2$	100 °C, 6 h	1,3-$(CH_3O_2CCH{=}CH)_2$-2-Br-5-$NO_2C_6H_2$ (34)
NO_2-4-Br-3,5-$I_2C_6H_2$	$C_6H_5C{\equiv}CH$	25 °C, 3 h	1,3-$(C_6H_5C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$ (59)
NO_2-4-Br-3,5-$I_2C_6H_2$	$HOC(CH_3)_2C{\equiv}CH$	25 °C, 4.5 h	1,3-$(HOC(CH_3)_2C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$ (71)
NO_2-4-Br-3,5-$(CH_3O_2CCH{=}CH)_2C_6H_2$	$HOC(CH_3)_2C{\equiv}CH$	25 °C, 4.5 h	1,3-$(CH_3O_2CCH{=}CH)_2$-2-$(HOC(CH_3)_2C{\equiv}C)$-5-$NO_2C_6H_2$ (21)
NO_2-3-Br-4,5-$I_2C_6H_2$	$C_6H_5C{\equiv}CH$	25–50 °C, 20 h	1,2-$(C_6H_5C{\equiv}C)_2$-3-Br-5-$NO_2C_6H_2$ (30)

[a] Ca. 1:1 mixture.

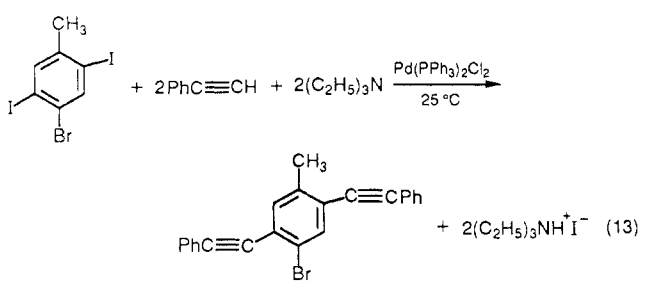
at 50 °C. Reduction products or other side products could not be isolated from the remaining viscous liquid product.

$$C_6I_6 + 6PhC{\equiv}CH + 6(C_2H_5)_3N \xrightarrow[CuI]{Pd(PPh_3)_2Cl_2} C_6(C{\equiv}CPh)_6 + 6(C_2H_5)_3NH^+I^- \quad (12)$$

1,2,4,5-Tetraiodobenzene gave the corresponding tetaphenylethynyl derivative in 63% yield at 25 °C in 12 h. Pentaiodotoluene and pentaiodobenzoic acid similarly produced the pentaphenylethynyl derivatives in 51% and 32% yields, respectively, at 50 °C.

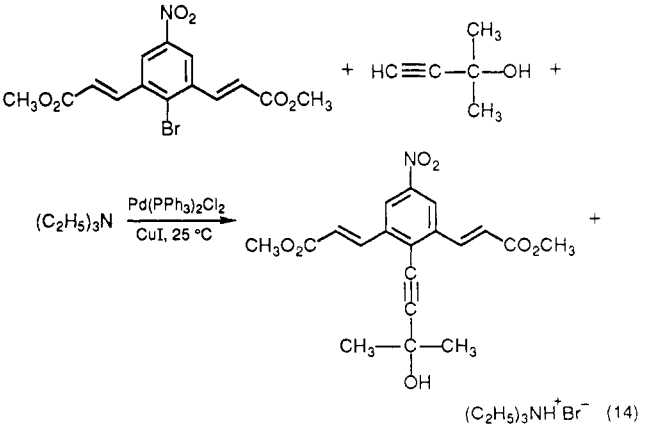
The triiodo compounds, 2,4,6-triiodophenol (62% yield), 2,4,5-triiodotoluene (87%), 3,4,5-triiodobenzoic acid (53%), and 3,4,5-triiodonitrobenzene (50%) all gave tris(phenylethynyl) derivatives in resonable yields at 25–50 °C. (Trimethylsilyl)acetylene reacted very poorly with the 3,4,5-triiodonitrobenzene (3% yield of tris alkynyl product) in agreement with Vollhardt's similar findings.[5]

Mixed bromoiodoaromatics were found to phenylethynylate more rapidly at the iodo positions, and some selective reactions were easily achieved. For example, 4-bromo-2,5-diiodotoluene in 4 h at 25 °C yielded 83% of the 1,4-diphenylethynyl derivative.



(13)

Likewise, 4-bromo-3,5-diiodonitrobenzene reacted with phenylacetylene and 2-methyl-3-butyn-2-ol to form the bromodialkynyl derivatives in 59% and 71% yield, respectively. 4-Bromo-3,5-bis[(methoxycarbonyl)ethenyl]-nitrobenzene, prepared by reaction of 4-bromo-3,5-diiodonitrobenzene with 2 equiv of methyl acrylate (see scheme), couples wih 2-methyl-3-butyn-2-ol at 25 °C to produce the alkynyl diester in 21% yield.



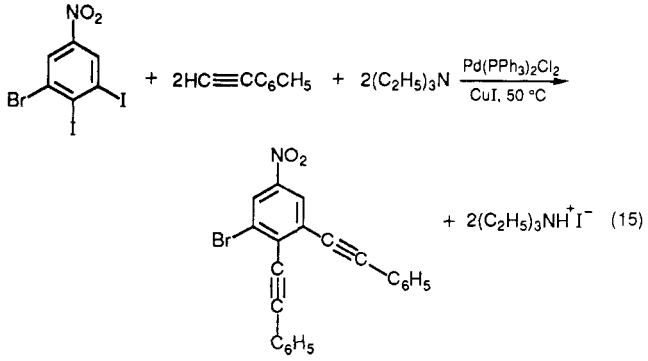
(14)

3-Bromo-4,5-diiodonitrobenzene reacted at 50 °C with phenylacetylene to form 3-bromo-1,2-bisphenylethynyl-5-nitrobenzene in 30% yield.

Attempts to selectively react 2-bromo-3,4,5,6-tetraiodo- and 3-bromo-2,4,5,6-tetraiodonitrobenzenes with phenylacetylene were unsuccessful. Mixtures of several products including partially dehalogenated compounds were formed, and pure products could not be isolated in either case.

Conclusions

Several polyiodoaromatic compounds with hydrogen, methyl, hydroxyl, carboxyl, or nitro substituents have been



(15)

found to undergo palladium-catalyzed alkenylation and alkynylation. Alkenylation, however, is only successful in cases where no more than two iodo groups are in adjacent positions. Alkynylation proceeds with all polyiodides tried in resonable yields to give the corresponding polyethynyl products.

Several polybromoiodides with methyl and nitro substituents were also alkenylated and alkynylated. Again, cis-alkenylation proceeded only when no more than two halogen groups were adjacent. Selective reactions of the iodo groups proved possible in the presence of bromo substituents when these conditions were met. Alkynylation occurred more readily and selectively with trihalo derivatives but not with pentahaloarenes. These reactions are useful for preparing a variety of 1,2,4,5-, 1,3,4,5-, and presumably 1,2,4,6-tetrasubtituted aromatics and some penta- and hexasubstituted derivatives as well.

Experimental Section

5-Bromo-2,4-diiodotoluene. A mixture of 1.59 g (6.97 mmol) of periodic acid and 5.20 g (20.5 mmol) of powdered iodine was added to 25 mL of concentrated sulfuric acid. The mixture was stirred at room temperature for 30 min and then cooled in an ice bath. *m*-Bromotoluene, 4.28 g (25 mmol), was then added, and stirring was continued overnight. The ice bath was allowed to melt and come to room temperature during this time. The red-brown reaction mixture was poured onto crushed ice, and the product was removed form the mixture by filtration. The crude product was washed well with water and recrystallized from ethanol twice to give 2.07 g (20%) of colorless needles, mp 87–89 °C. The ^{1}H NMR spectral data is given in Table II.

4-Bromo-2,5-diiodotoluene. A mixture of 1.59 g (6.97 mmol) periodic acid and 5.20 g (20.5 mmol) of powdered iodine was stirred with 25 mL of concentrated sulfuric acid for 30 min. The black solution then was cooled to 0 °C, 4.28 g (25 mmol) of melted *p*-bromotoluene was added, and the mixture was stirred and allowed to warm up to room temperature. After being stirred overnight the semisolid mixture was poured onto ice, and the red-brown solid was separated by filtration and washed thoroughly with water. After air drying, the crude product was distilled under reduced pressure. The fraction bp 150–160 °C (0.6 mm) quickly solidified, and it was recrystallized from ethanol to yield 3.37 (32%) of long needles, mp 97–98 °C. A second crop of 0.72 g (7%), mp 95–97 °C, was obtained by concentrating the mother liquors. Physical properties are given in Table II.

6-Bromo-2,3,4,5-tetraiodotoluene. A solution of 2.25 g (9.87 mmol) of periodic acid and 5.55 g (21.87 mmol) of powdered iodine in 25 mL of concentrated sulfuric acid was stirred at room temperature for 30 min and then cooled to 0 °C when 1.35 mL (10.89 mmol) of *o*-bromotoluene was added. The mixture was stirred overnight, allowing the ice bath to come to room temperature. The reaction mixture was poured onto crushed ice, and the solid formed was separated by filtration. After a thorough washing with water the product was recrystallized twice from DMSO. There was obtained 2.71 g (37%) of yellow needles, mp >300 °C. The ^{1}H NMR spectrum in DMSO showed a single peak at 2.17 ppm. Mol wt (HRMS): found 673.56, calcd 673.56.

5-Bromo-2,3,4,6-tetraiodotoluene. This compound was prepared exactly as the 6-bromo-2,3,4,5-tetraiodotoluene above, employing *m*-bromotoluene in place of *o*-bromotoluene. Recrystallization from DMSO gave yellow needles, mp >290 °C ^{1}H NMR (DMSO): δ 2.20 (singlet). Mol wt (HRMS): found 673.56, calcd 673.56.

2,5-Dibromo-4-iodotoluene. To a solution of 35.0 g (0.22 mmol) of bromine in 50 mL of carbon tetrachloride was added a few milligrams of ferric chloride followed by 21.8 g (0.10 mol) of *p*-iodotoluene. The solution was heated to reflux on a steam bath under a condenser with a drying tube attached. After heating overnight the reaction mixture was distilled under vacuum. The product, bp 120–130 °C (0.4 mm), solidified as it was being distilled. Two recrystallizations of the distillate from hexane yielded 18.0 g (48%) of dibromide, mp 96–97.5 °C. The ^{1}H NMR spectral data of the product appears in Table II.

4-Bromo-3,5-diiodonitrobenzene. A mixture of 1.59 g (6.97 mmol) of periodic acid and 5.20 g (20.5 mmol) of powdered iodine was stirred with 25 mL of concentrated sulfuric acid for 30 min, and 4.04 g (20 mmol) of powdered *p*-bromonitrobenzene was added. The mixture was then warmed with stirring to 75–80 °C and kept at this temperature overnight. After cooling, the mixture was poured onto ice, and the product was removed by filtration. After washing well with water the product was recrystallized twice from ethanol. There was obtained 3.95 g (44%) of yellow-brown needles, mp 129.5–130.5 °C. The ^{1}H NMR spectral data is given in Table II.

3-Bromo-4,5-diiodonitrobenzene. ***m*-Bromonitrobenzene** was diiodinated as in the preceding example. The crude material did not solidify, so it was extracted from the ice water solution with methylene chloride. The extracts were washed with ice water and aqueous sodium bisulfite and then concentrated to a yellow, viscous oil. The product was dissolved in 100 mL of hot methanol, and on cooling yellow crystals were obtained. A second recrystallization from methanol gave only an 8% yield of pale yellow needles of the product, mp 140–142 °C. The ^{1}H NMR spectral data appears in Table II.

General Procedure for Alkenylation of Polyhalides. In a 15-mL thick-walled Pyrex tube is placed 0.1 mmol of $Pd(OAc)_2$, 0.2 mmol of triphenylphosphine, 2 mmol of a monoiodide (1 mmol of a diiodide, etc., in proportion to the number of iodo groups to be reacted), 2.2–5.0 mmol of the alkene, and 8 mL of triethylamine. The tube is capped and shaken until the mixture is homogeneous (warm if necessary). The solution is then heated at 100 °C for the times indicated in Table I. After cooling the reactions mixtures are stirred with ice and hydrochloric acid, and the products are extracted with methylene chloride. After drying over $MgSO_4$ the solvent is removed under reduced pressure, and the residue is recrystallized or chromtographed on silica. The products prepared by this procedure are listed in Table I.

General Procedure for the Alkynylation of Polyhalides. A mixture of 0.02 mmol of $Pd(PPh_3)_2Cl_2$, 1.0 mmol of a monohalide (0.5 mmol of a dihalide, etc., in proportion to the number of halo groups to be reacted), 1.1–2.3 mmol of the alkyne, ~50 mg of cuprous iodide, and 6–8 mL of triethylamine is stirred under the conditions given in Table I. If the halide is insoluble in triethylamine, 2–5 mL of the amine may be replaced by DMSO. The products are generally isolated as described above for the alkenylations. (See following example).

Hexakis(phenylethynyl)benzene. A mixture of 2.46 g (24 mmol) phenylacetylene, 0.088 g (0.12 mmol) of $(PPh_3)_2PdCl_2$, ~50 mg of cuprous iodide, 10 mL of triethylamine, and 2 mL of DMSO was stirred magnetically in an Erylenmeyer flask overnight at 50 °C. The yellow solid which precipitated was separated by filtration and purified by two recrystallizations from methylene chloride–ethanol. There was isolated 0.72 g (53%) of yellow needles of the product. Properties are given in Table II.

Methyl (*E*)-4-Methyl-2,5-dibromocinnamate. A mixture of 3.75 g (10 mmol) of 2,5-dibromo-4-iodotoluene, 0.046 g (0.2 mmol) of palladium acetate, 1.03 g (12 mmol) of methyl acrylate, and 20 mL of triethylamine was prepared in a thick-walled Pyrex tube, and the tube was capped. The mixture was shaken and warmed until it was homogeneous and then heated at 100 °C overnight. After cooling, the solution solidified. Cold dilute hydrochloric acid was mixed with the solid, and the product was separated by filtration. The solid was water washed and recrystallized twice from methanol with hot filtration through Celite to remove finely divided palladium metal. There was obtained

Table II. Properties of Compounds Prepared

compound	mp, °C	^{1}H NMR ($CDCl_3$)	mol wt or anal. (calcd value)
1,2,4,5-$(CH_3O_2CCH{=}CH)_4C_6H_2$	224–225	7.96 (d, J = 15.8 Hz, 4 H), 7.75 (s, 2 H), 6.42 (d, J = 15.8, 4 H), 3.84 (s, 12 H)	414.70 (414.71)
1,2,4-$(CH_3O_2CCH{=}CH)_3C_6H_3$	129–130	8.02 (d, J = 15.9, 1 H), 7.99 (d, J = 15.9, 1 H), 7.67 (d, J = 16.1, 1 H), 7.64 (d, J = 8.0, 1 H), 7.59 (s, 1 H), 7.55 (d, J = 8.0, 1 H), 6.50 (d, J = 16.1, 1 H), 6.40 (d, J = 15.8, 1 H), 6.38 (d, J = 15.8, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H)	330.39 (330.38)
1,4-$CH_3O_2CCH{=}CH)_2C_6H_4$	120–121	7.68 (d, J = 16.0, 2 H), 7.55 (s, 4 H), 6.46 (d, J = 16.0, 2 H), 3.82 (s, 6 H)	246.11 (246.11)
1,2,3,4,5,6-$(C_6H_5C{\equiv}C)_6C_6$	169–170	7.34–7.67 (m, 30 H)	C, 95.52; H, 4.48 (C, 95.54; H, 4.46)
1,2,4,5-$(C_6H_5C{\equiv}C)_4C_6H_2$	193–194	7.78 (s, 2 H), 7.60–7.34 (m, 20 H)	478.72 (478.72)
1,2-$(CH_3O_2CCH{=}CH)_2C_6H_4$	65–66	8.04 (d, J = 15.8, 2 H), 7.58 (dd, J = 5.6, 3.4, 2 H), 7.40 (dd, J = 5.8, 3.4, 2 H), 6.36 (d, J = 15.7, 2 H), 3.83 (s, 6 H)	246.11 (246.11)
HO-2,4,6-$(C_6H_5C{\equiv}C)_3C_6H_2$	141–142	7.93–7.89 (m, 2 H), 7.73–7.34 (m, 15 H), 7.01 (s, 1 H)	394.14 (394.14)
CH_3-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$	193–194	7.43–7.35 (m, 30 H), 2.40 (s, 3 H)	C, 95.22; H, 4.76 (C, 95.23; H, 4.71)
CH_3-2,4,5-$(CH_3O_2CCH{=}CH)_3C_6H_2$	140–142	7.96 (d, J = 15.8, 1 H), 7.95 (d, J = 16.0, 1 H), 7.91 (d, J = 16.0, 1 H), 7.72 (s, 1 H), 7.42 (s, 1 H), 6.43 (d, J = 15.9, 1 H), 6.38 (d, J = 16.0, 1 H), 6.36 (d, J = 15.9, 1 H), 3.83 (s, 9 H), 2.46 (s, 3 H)	344.13 (344.13)
$CH_3(CH_3O_2CCH{=}CH)_2C_6H_3$	124–125	7.94 (d, J = 15.8, 1 H), 7.64 (d, J = 16.0, 1 H), 7.57 (d, J = 8.0, 1 H), 7.37 (d, J = 8.2, 1 H), 7.35 (s, 1 H), 6.46 (d, J = 15.6, 1 H), 6.40 (d, J = 15.5, 1 H), 3.82 (s, 6 H), 2.46 (s, 3 H)	260.12 (260.12)
CH_3-2,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$	152–153	7.71 (s, 1 H), 7.51–7.59 (m, 6 H), 7.43 (s, 1 H), 7.43 (s, 1 H), 7.31–7.37 (m, 9 H), 2.51 (s, 3 H)	392.16 (392.16)
HO_2C-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$	193–194	7.89–7.26 (m, 30 H), 2.72 (b s, 1 H)	C, 90.63; H, 4.16 (C, 90.64; H, 4.18)
HO_2C-3,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$	240 dec	8.09[a] (s, 2 H), 7.66–7.42 (m, 15 H), 3.16 (s, 1 H)	422.13 (422.13)
1,2,3-$(C_6H_5C{\equiv}C)_3$-5-$NO_2C_6H_2$	164–165	8.30 (s, 2 H), 7.58–7.64 (m, 5 H), 7.42–7.34 (m, 10 H)	423.13 (423.13)
1,2,3-$[(CH_3)_3SiC{\equiv}C]_3$-5-$NO_2C_6H_2$	180–181	8.21 (s, 2 H), 0.32 (s, 9 H), 0.29 (s, 18 H)	C, 59.36; H, 3.31 (C, 59.37; H, 3.32)
CH_3-2-Br-4,5-$I_2C_6H_2$	104–105	7.92 (s, 1 H), 7.67 (s, 1 H), 2.28 (s, 3 H)	421.77 (421.77)
CH_3-5-Br-2,4-$I_2C_6H_2$	87–89	8.20 (s, 1 H), 7.44 (s, 1 H), 2.35 (s, 3 H)	421.77 (421.77)
CH_3-4-Br-2,5-$I_2C_6H_2$	97–98	7.98 (s, 1 H), 7.68 (s, 1 H), 2.30 (s, 3 H)	421.77 (421.77)
CH_3-2,5-Br_2-4-IC_6H_2	96.0–97.5	7.96 (s, 1 H), 7.47 (s, 1 H), 2.30 (s, 3 H)	373.78 (373.78)
$(CH_3O_2CH{=}CH)$-2,5-Br_2-4$CH_3C_6H_2$	132.5–134.0	7.91 (d, J = 17, 1 H), 7.74 (s, 1 H), 7.48 (s, 1 H), 6.35 (d, J = 17, 1 H), 3.82 (s, 3 H), 2.38 (s, 3 H)	331.90 (331.90)
NO_2-4-Br-3,5-$I_2C_6H_2$	129.5–130.5	8.66 (s, 2 H)	452.74 (452.74)
NO_2-3-Br-4,5-$I_2C_6H_2$	140–142	8.59 (d, J = 2.5, 1 H), 8.42 (d, J = 2.5, 1 H)	452.74 (452.74)
1,4-$(C_6H_5C{\equiv}C)_2$-5-Br-2-$CH_3C_6H_2$	133.5–134.5	7.73 (s, 1 H), 7.60–7.50 (m, 4 H), 7.41 (s, 1 H), 7.38–7.34 (m, 6 H), 2.45 (s, 3 H)	370.04 (370.04)
$(CH_3O_2CCH{=}CH)$-2,5-$(C_6H_5CH{=}CH)_2$-4-$CH_3C_6H_2$	148–149	8.15 (d, J = 18, 1 H), 7.80 (s, 1 H), 7.58–7.25 (m, 15 H), 7.08 (d, J = 12, 1 H), 7.08 (d, J = 12, 1 H), 7.00 (d, J = 11, 1 H), 6.48 (d, J = 18, 1 H), 3.83 (s, 3 H), 2.47 (s, 3 H)	380.18 (380.18)
$(CH_3COCH_2CH_2)$-2,5-Br_2-4-$CH_3C_6H_2$	50–52	7.41 (s, 1 H), 7.40 (s, 1 H), 2.92 (t, J = 7, 2 H), 2.74 (t, J = 7, 2 H), 2.34 (s, 3 H), 2.16 (s, 3 H)	320.[b] (320.)
1,3-$(CH_3OCCH{=}CH)_2$-2-Br-5-$NO_2C_6H_2$	250 dec	8.61 (s, 2 H), 7.96 (d, J = 16, 2 H), 6.90 (d, J = 16, 2 H), 3.78 (s, 6 H)	368.98 (368.98)
1,3-$(C_6H_5C{\equiv}C{-})_2$-2-Br-5-$NO_2C_6H_2$	159–160	8.29 (s, 2 H), 7.67–7.57 (m, 4 H), 7.46–7.36 (m, 6 H)	401.01 (401.01)
1,3-$(HOC(CH_3)_2C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$	164–165	8.16 (s, 2 H), 2.29 (s, 2 H), 1.66 (s, 12 H)	C, 52.36; H, 4.35 (C, 52.47; H, 4.40)
1,3-$(CH_3O_2CCH{=}CH)_2$-2-$(HOC(CH_3)_2C{\equiv}C)$-5-$NO_2C_6H_2$	210–214 dec	8.42 (s, 2 H), 8.17 (d, J = 18, 2 H), 6.65 (d, J = 18, 2 H), 3.87 (s, 6 H), 2.75 (s, 1 H), 1.73 (s, 6 H)	C, 60.38; H, 5.18 (C, 61.12; H, 5.13)
1,2-$(C_6H_5C{\equiv}C)_2$-3-Br-5-$NO_2C_6H_2$	128–129	8.42 (d, J = 2.5, 1 H), 8.33 (d, J = 2.5, 1 H), 7.63 (m, 4 H), 7.40 (m, 6 H)	

[a] In DMSO-d_6 solution. [b] Parent ion was too weak for precise mass measurement.

2.70 g (81%) of off-white crystals, mp 132.5–134 °C. The ^{1}H NMR spectral data is given in Table II.

Methyl (*E*)-4-Methyl-2,5-bis(phenylethenyl)cinnamate. A mixture of 0.5 g (1.5 mmol) of methyl (*E*)-4-methyl-2,5-dibromocinnamate, 0.023 g (0.1 mmol) of palladium acetate, 0.060 g (0.2 mmol) of tri-*o*-tolylphosphine, 0.53 g (5.1 mmol) of styrene, and 4 mL of triethylamine was prepared in a thick-walled Pyrex tube. After capping, the tube was warmed and shaken until it was homogeneous, and then it was heated at 100 °C overnight. The reaction mixture was cooled and diluted with cold dilute hydrochloric acid. The solid formed was removed by filtration, water-washed, and air-dried. The crude product was then recrystallized from methylene chloride–methanol. Yellow-orange crystals, 0.26 g (46%), were obtained. Properties are listed in Table II.

4-(2,5-Dibromo-4-methylphenyl)-2-butanone. A mixture of 0.02 g (0.10 mmol) of palladium acetate, 1.88 g (5 mmol) of 2,5-dibromo-4-iodotoluene, 0.43 g (6 mmol) of 3-buten-2-ol, 2 mL of triethylamine, and 8 mL of acetonitrile was prepared in a thick-walled Pyrex tube, and the tube was capped. The tube was warmed and shaken until the solution was homogeneous, and then it was heated at 100 °C overnight. The cooled reaction mixture was diluted with cold, dilute hydrochloric acid, and the product was extracted with ether. The extracts were washed with water and aqueous sodium bicarbonate. The solution was dried ($MgSO_4$), concentrated, and distilled under reduced pressure. The fraction bp 110–160 °C (1.5 mm) solidified on standing (1.29 g, 71%). Recrystallization from pentane gave 0.59 g (37%) of product, mp 42–46 °C, which was quite pure by ^{1}H NMR analysis. Another recrystallization from pentane gave 0.36 g (22%) of product, mp 50–52 °C. The spectral data is given in Table II.

2-Bromo-1,3-bis(3-hydroxy-3-methyl-1-butynyl)-5-nitrobenzene. A mixture of 0.042 g of $(PPh_3)_2PdCl_2$ (0.06 mmol), 1.36 g (3 mmol) of 4-bromo-3,5-diiodonitrobenzene, 0.53 g (6.3 mmol) of 2-methyl-3-butyn-2-ol, and 12 mL of triethylamine was stirred magnetically, and ~50 mg of cuprous iodide was added. Stirring at room temperature was continued for 4.5 h. The solution then was diluted with ice and cold, dilute hydrochloric acid, and the precipitated product was removed by filtration. The solid was washed well with water and air-dried. The crude product was purified by chromatography on silica gel. A final recrystallization from chloroform–hexane gave 0.78 g (71%) of off-white crystals,

mp 164–165 °C. The ^1H NMR spectral data is given in Table II.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. *m*-$BrC_6H_4CH_3$, 591-17-3; *p*-$BrC_6H_4CH_3$, 106-38-7; *o*-$BrC_6H_4CH_3$, 95-46-5; *p*-$BrC_6H_4NO_2$, 586-78-7; *m*-$BrC_6H_4NO_2$, 585-79-5; *p*-$IC_6H_4CH_3$, 624-31-7; Me-5-Br-2,4-$I_2C_6H_2$, 123568-17-2; Me-4-Br-2,5-$I_2C_6H_2$, 123568-18-3; Me-6-Br-2,3,4,5-I_4C_6, 123568-19-4; Me-5-Br-2,3,4,6-I_4C_6, 123568-20-7; Me-2,5-Br_2-4-IC_6H_2, 123568-21-8; NO_2-4-Br-3,5-$I_2C_6H_2$, 6311-50-8; NO_2-3-Br-4,5-$I_2C_6H_2$, 98137-95-2; I_6C_6, 608-74-2; 1,2,4,5-$I_4C_6H_2$, 636-31-7; 1,4-$I_2C_6H_4$, 624-38-4; 1,2-$I_2C_6H_4$, 615-42-9; HO-2,4,6-$I_3C_6H_2$, 609-23-4; $CH_3I_5C_6$, 64349-91-3; Me-2,4,5-$I_3C_6H_2$, 32704-10-2; Me-2-Br-4,5-$I_2C_6H_2$, 123568-22-9; HO_2C-2,3,4,5,6-I_5C_6, 64385-02-0; HO_2C-3,4,5-$I_3C_6H_2$, 2338-20-7; NO_2-3,4,5-$I_3C_6H_2$, 53663-23-3; $MeO_2CCH{=}CH_2$, 96-33-3; HC≡CPh, 536-74-3; $CH_2{=}CHPh$, 100-42-5; $CH_2{=}CHCH(OH)CH_3$, 598-32-3; $(CH_3)_3SiC{\equiv}CH$, 1066-54-2; $HOC(CH_3)_2C{\equiv}CH$, 115-19-5; $Pd(OAc)_2$, 3375-31-3; $Pd(PPh_3)_2Cl_2$, 13965-03-2; (*E*)-2,5-Br_2-4-CH_3-1-$(CH_3O_2CCH{=}CH)C_6H_2$, 123568-23-0; N-O_2-4-Br-3,5-$(CH_3O_2CCH{=}CH)_2C_6H_2$, 123568-24-1; 1,2,4,5-$(CH_3O_2CCH{=}CH)_4C_6H_2$, 123568-25-2; 1,2,4-$(CH_3O_2CCH{=}CH)_3C_6H_3$, 123568-26-3; 1,4-$(CH_3O_2CCH{=}CH)_2C_6H_4$, 7549-44-2; 1,2,3,4,5,6-$(C_6H_5C{\equiv}C)_6C_6$, 110846-75-8; 1,2,4,5-$(C_6H_5C{\equiv}C)_4C_6H_2$, 25634-84-8; 1,2-$(CH_3O_2CCH{=}CH)_2C_6H_4$, 61198-30-9; HO-2,4,6-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-27-4; Me-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$, 123568-28-5; Me-2,4,5-$(CH_3O_2CCH{=}CH)_3C_6H_2$, 123568-29-6; Me-2,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-30-9; 3-Br-4-$CH_3C_6H_3CH{=}CHC_6H_5$, 123568-31-0; 4-Br-3-$CH_3C_6H_3CH{=}CHC_6H_5$, 123568-32-1; 1,3-$(CH_3O_2CCH{=}CH)_2$-4-Br-6-$CH_3C_6H_2$, 123568-33-2; 1,4-$(C_6H_5C{\equiv}C)_2$-5-Br-2-$CH_3C_6H_2$, 123568-34-3; $(CH_3COCH_2C-H_2)$-2,5-Br_2-4-$CH_3C_6H_2$, 123568-35-4; $(CH_3O_2CCH{=}CH)$-2,5-$(C_6H_5CH{=}CH)_2$-4-$CH_3C_6H_2$, 123568-36-5; HO_2C-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$, 123568-37-6; HO_2C-3,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-38-7; 1,2,3-$(C_6H_5C{\equiv}C)_3$-5-$NO_2C_6H_2$, 123568-39-8; 1,2,3-$((CH_3)_3SiC{\equiv}C)_3$-5-$NO_2C_6H_2$, 123568-40-1; 1,3-$(C_6H_5C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$, 123568-41-2; 1,3-$(HOC(CH_3)_2C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$, 123568-42-3; 1,3-$(CH_3O_2CCH{=}CH)_2$-2-$(HOC-(CH_3)_2C{\equiv}C)$-5-$NO_2C_6H_2$, 123568-43-4; 1,2-$(C_6H_5C{\equiv}C)_2$-3-Br-5-$NO_2C_6H_2$, 123568-44-5; $Me(CH_3O_2CCH{=}CH)_2C_6H_3$, 123568-47-8; $I_5C_6NO_2$, 59875-34-2; NO_2-3,5-$(CH_3O_2CCH{=}CH)_2C_6H_3$, 20883-29-8; NO_2-2-Br-3,4,5,6-I_4C_6, 123568-45-6; NO_2-3-Br-2,4,5,6-I_4C_6, 123568-46-7.

Lithiation of Methoxypyridines Directed by α-Amino Alkoxides

Daniel L. Comins*,[1] and Michael O. Killpack

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300

Received June 13, 1989

The addition of methoxypyridinecarboxaldehydes to certain lithium dialkylamides gave α-amino alkoxides in situ that were ring-lithiated with alkyllithium bases. Alkylation and hydrolysis on workup provided ring-substituted methoxypyridinecarboxaldehydes via a one-pot reaction. The one-pot methylation of isomeric methoxypyridinecarboxaldehydes was examined. The regioselectivity of the lithiation–methylation was dependent on the aldehyde, the amine component of the α-amino alkoxide, and the metalation conditions. When lithiated *N,N,N'*-trimethylethylenediamine was used as the amine component of the α-amino alkoxide, methylation generally occurred ortho to the aldehyde function. The analogous reactions using lithium *N*-methylpiperazide as the amine component gave substitution next to the methoxy group. Several new methylated methoxypyridinecarboxaldehydes were prepared in a regioselective manner by using this one-pot procedure.

Despite the susceptibility of pyridines to nucleophilic attack by alkyllithium bases, directed lithiation has recently evolved as a useful method for regioselective substitution of the pyridine ring.[2] A variety of ortho-directing groups have been utilized to effect regiospecific metalation into an ortho position of pyridine. Directing groups include $CONR_2$,[3] CONHR,[3] oxazolines,[4] pivaloylamino,[5] $OCONEt_2$,[6] OR,[7] OCH_2OR,[8] halogen,[9] and SO_2NR_2.[10] Carbonyl-derived directing groups prepared from pyridinecarboxaldehydes have not been investigated. Due to a need for substituted methoxypyridinecarboxaldehydes in our laboratories, we decided to study the lithiation of methoxypyridines directed by α-amino alkoxides.

The addition of aromatic aldehydes to certain lithium dialkylamides gives α-amino alkoxides that can be ring-lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction. This methodology works well for the one-pot substitution of benzaldehyde derivatives[11] as well

(1) Address correspondence to this author at Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204.

(2) For reviews, see: Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199. Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.

(3) Epsztajn, J.; Bieniek, A.; Brzezin'ski, J. Z.; Jo'z'wiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735. Epsztajn, J.; Brzezin'ski, J. Z.; Jo'z'wiak, A. *J. Chem. Res., Synop.* **1986**, 18. Epsztajn, J.; Bieniek, A.; Plotka, M. W. *Ibid.* **1986**, 20.

(4) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, *19*, 227. Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133.

(5) Tamura, Y.; Fujita, M.; Chen, L.; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564. Turner, J. A. *Ibid.* **1983**, *48*, 3401. Güngör, T.; Marsais, F.; Quéguiner, G. *Synthesis* **1982**, 499.

(6) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

(7) (a) Marsais, F.; Le Nard, G.; Quéguiner, G. *Synthesis* **1982**, 235. (b) Wada, A.; Kanatomo, S.; Nagai, S. *Chem. Pharm. Bull.* **1985**, *33*, 1016. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773. (d) Trécourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367.

(8) Winkle, M. R.; Ronald, R. D. *J. Org. Chem.* **1982**, *47*, 2101.

(9) Mallet, M.; Marsais, F.; Quéguiner, G.; Pastour, P. *C. R. Acad. Sci. Ser. C* **1972**, *275*, 1439. Mallet, M.; Marsais, F.; Quéguiner, G.; Pastour, P. *Ibid.* **1972**, *275*, 1535. Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139. Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. Marsais, F.; Lapendrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Miniprint*, **1982**, 2863. Marsais, F.; Trécourt, F.; Breânt, P.; Quéguiner, G. *J. Heterocycl. Chem.* **1988**, *25*, 81. Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.

(10) Breânt, P.; Marsais, F.; Quéguiner, G. *Synthesis* **1982**, 822. Marsais, F.; Cronnier, A.; Trécourt, F.; Quéguiner, G. **1987**, *52*, 1133.

(11) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. Comins, D. L.; Brown, J. D. *Ibid.* **1983**, *24*, 5465. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. Comins, D. L.; Brown, J. D. *Ibid.* **1989**, *54*, 3730.

0022-3263/90/1955-0069$02.50/0