A One-Pot Synthesis of *m*-Terphenyls via a Two-Aryne Sequence

Chi-Jen Frank Du,† Harold Hart,* and Kwok-Keung Daniel Ng

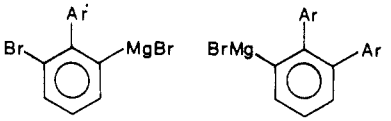
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received January 10, 1986

Aryl-Grignards (3^+ equiv) react with 2,6-dibromoiodobenzene or other 1,2,3-trihalobenzenes to give 2,6-diarylphenylmagnesium halides. The mechanism involves Grignard exchange at the central halogen, followed by two cycles of magnesium halide loss and regioselective capture of the resulting aryne by the aryl-Grignard reagent (Scheme I). Typical examples are shown in Table I. The method is especially applicable to *m*-terphenyls in which the "outer" rings are identical and/or in which substitution at the 2′ or other positions of the "central" ring is desired.

We describe here a one-pot route to *m*-terphenyls from the reaction of a 1,2,3-trihalobenzene with excess aryl-Grignard reagent. This new method developed logically from our recent papers on multiple carbon–carbon bond construction via the creation and capture of arynes with Grignard reagents.[1,2]

We reasoned that 2,6-dibromoiodobenzene (**1**)[3] would undergo halogen–metal exchange preferentially at iodine to give Grignard **2** (Scheme I). If this mono-Grignard would form aryne **3**, trapping should give **4** rather than its regioisomer **4′**. Nucleophilic additions to 3-bromobenzyne



4′ **6′**

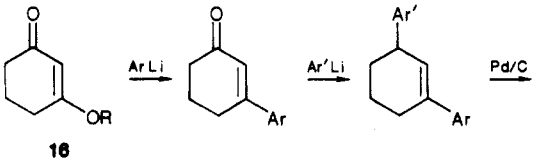
are known to occur predominantly in this manner as a consequence of electron withdrawal by the bromine substituent.[3,4] This addition mode would set the stage for a second aryne reaction, and the resulting 3-arylaryne **5** should again add the nucleophile meta to give **6** instead of **6′**, probably for both electronic and steric reasons.[5-7] In the event, these predictions were fulfilled.

Results and Discussion

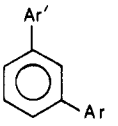
2,6-Dibromoiodobenzene (**1**)[8] was readily prepared in quantity from 2,6-dibromoaniline[9] via diazotization and treatment with potassium iodide. A solution of **1** in THF was added dropwise to somewhat over the theoretical 3 equiv of aryl-Grignard in the same solvent, usually at room temperature but in some instances at reflux. After additional stirring for a few hours, the mixture was quenched with dilute aqueous acid. Results are summarized in Table I.

In general, the yields of *m*-terphenyl are quite good, the only poor example being entry 7. 1,2,3-Tribromobenzene and 2,6-dichloroiodobenzene, in place of **1**, gave somewhat lower, but still good, yields of **7** with phenylmagnesium bromide. The product structures were clear from spectral data and from comparison of melting points with literature values, except for **8**, **12**, and **13** which are new.

The value of our method can be seen by comparison with literature syntheses of the known compounds in Table I. *m*-Terphenyl itself is, of course, commercially available, but other examples in Table I are not. Woods developed the best general route to *m*-diarylbenzenes, via the enol ether of dihydroresorcinol.[10] Using this three-step sequence, with Ar = Ar′ = *p*-biphenyl, he obtained a 72% yield of **9**;[11] our yield is comparable and requires only one step. In other cases, his method gave significantly lower



16



17

yields than ours (for **10**, 17%;[12] for **11**, <18%;[13] for **14** and **15**, 23%[14]).

The advantage of the Woods synthesis is that the added "external" aryl rings may be different from one another since they are incorporated stepwise. In this sense, it is a more versatile method than ours. On the other hand, if the two "external" rings are identical, our synthesis is shorter and generally gives superior yields.

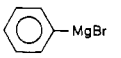
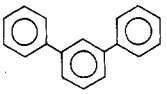
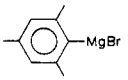
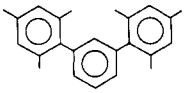
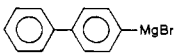
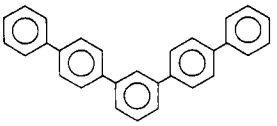
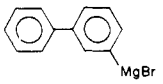
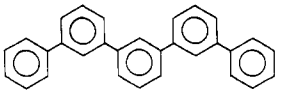
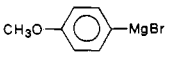
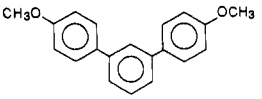
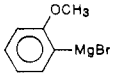
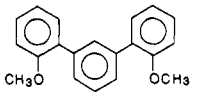
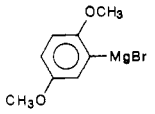
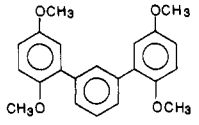
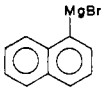
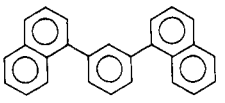
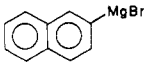
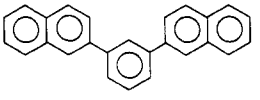
Another advantage of our method is that substituents are easily incorporated on the "central" ring. The actual reaction product is the *m*-terphenyl-Grignard **6** which, in principle, can be treated with various electrophiles other than the proton. In practice, this may lead to difficultly separable mixtures because some excess or unreacted aryl-Grignard reagent is present and will also react with the added electrophile. Quenching with a halogen (bro-

† Dow Chemical Company Fellow at MSU, 1985–86.

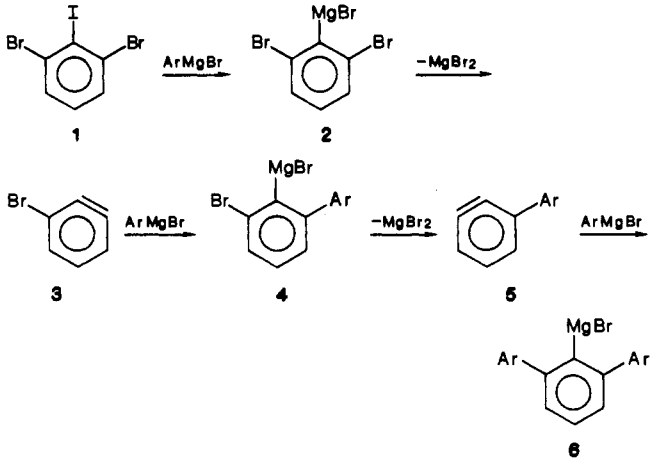
(1) Hart, H.; Harada, K.; Du, C.-J. F. *J. Org. Chem.* **1985**, *50*, 3104. Hart, H.; Harada, K. *Tetrahedron Lett.* **1985**, *26*, 29.
(2) Harada, K.; Hart, H.; Du, C.-J. F. *J. Org. Chem.* **1985**, *50*, 5524.
(3) Huisgen, R. In *Organometallic Chemistry*; Zeiss, H., Ed.; Reinhold Publishing Corp.: New York; 1960, p 78.
(4) Wotiz, J. H.; Huba, F. *J. Org. Chem.* **1959**, *24*, 595.
(5) Wittig, G.; Merkle, W. *Chem. Ber.* **1942**, *75*, 1491.
(6) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91.
(7) In a closely related example, 2,6-diphenylbenzoic acid was obtained from 2-fluorobiphenyl and excess phenyllithium followed by a CO_2 quench; Jones, D. H.; Wragg, W. R. *J. Chem. Soc. C* **1968**, 2154.
(8) Bolton, R.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1977**, 278.
(9) Seikel, M. K. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 262.
(10) Other methods include the Ullmann reaction, rearrangement of *o*- or *p*-terphenyls with aluminum chloride, Fittig-type reactions of 1,3-dihalobenzenes, and so on. None of these is as generally or satisfactorily applicable as the Woods method. For a brief survey, see: Cheeseman, G. W. H.; Praill, P. F. G. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Elsevier: Amsterdam, 1974; Vol. III^F, p 54.
(11) Woods, G. F.; Tucker, I. W. *J. Am. Chem. Soc.* **1948**, *70*, 3340.
(12) Woods, G. F.; Reed, F. T. *J. Am. Chem. Soc.* **1949**, *71*, 1348.
(13) Mueller, G. P.; Honaker, C. B. *J. Am. Chem. Soc.* **1951**, *73*, 2377.
(14) Woods, G. F.; Reed, F. T.; Arthur, T. E.; Ezekiel, H. *J. Am. Chem. Soc.* **1951**, *73*, 3854.
(15) These trihalobenzenes were prepared by procedures analogous to those given for **14**.

0022-3263/86/1951-3162$01.50/0

Table I. *m*-Terphenyls from 1 and Aryl-Grignards

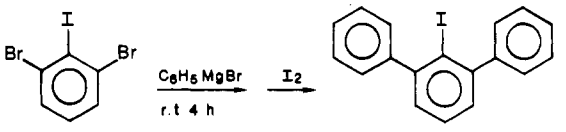
entry	ArMgBr	conditions	product	yield (%)
1		rt, 3 h	 7	77
2		rt, 3 h	 8	70
3		rt, 5 h	 9	73
4		rt, 5 h	 10	62
5		rt, 5 h	 11	80
6		reflux, 10 h	 12	85
7		reflux, 10 h	 13	25
8		rt, 5 h	 14	57
9		rt, 5 h	 15	64

Scheme I



mine or iodine), however, works well. For example, 2′-iodo-*m*-terphenyl (18) was obtained in 88% yield from 1 and phenylmagnesium bromide, using an iodine quench.

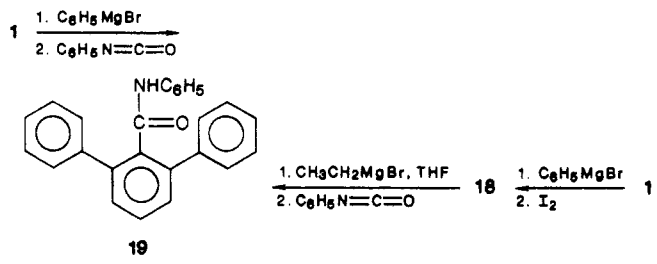
This route to 18 is superior to a three-step literature route involving an Ullmann cross-coupling.[16] Of course, 18 or



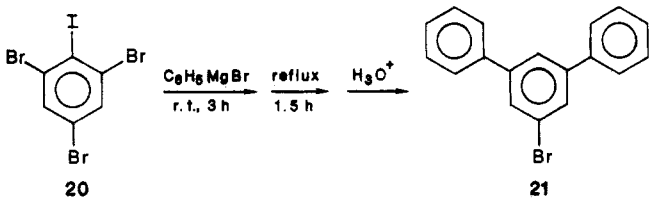
analogous *m*-terphenyls can then be reconverted to Grignard reagents 6 and treated with other electrophiles. This two-step sequence is sometimes cleaner and preferable to direct quenching with complex electrophiles. For example, quenching of the reaction of 1 and phenylmagnesium bromide with phenyl isocyanate gave anilide 19 in one step and 63% yield. The same product was obtained in two steps from 1 via iodoarene 18 in higher overall yield (88% × 85% = 75%) and with easier workup.

Substituents can also be incorporated elsewhere in the "central" ring by starting with an appropriately substituted

(16) Ibuki, E.; Ozasa, S.; Fujioka, Y.; Mizutani, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 845.



1. For example, tribromoiodobenzene **20** was readily converted to 5′-bromo-*m*-terphenyl (**21**) in good yield.



In summary, we have described a new broadly useful route to *m*-terphenyls. Unique features of the synthesis are (a) both "outer" rings of the terphenyl are derived from the Grignard reagent and are, therefore, identical; (b) the central ring is derived from the trihalobenzene and has an organometallic function on that ring at the carbon atom *between* the two carbons to which the "outer" aryl rings are attached; this position can, therefore, be elaborated with various electrophiles; (c) the reaction occurs via two successively formed aryne intermediates, and (d) the method is characterized by high yields, simplicity and versatility. Extensions to other types of Grignard reagents (vinyl, heterocyclic, ethynyl) will be the subject of future reports.

Experimental Section

General Procedures. ^1H NMR spectra were determined on a Varian T-60 or Bruker WM-250 spectrometer in $CDCl_3$ solution containing $(CH_3)_4Si$ as an internal standard. Chemical shifts are reported in δ units. Mass spectra were recorded at 70 eV on a Finnigan 4000 spectrometer operated by Richard Olsen. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Anhydrous magnesium sulfate was the drying reagent throughout, and the silica gel for chromatography was 230–400 mesh; some separations were performed on a Chromatotron (Harrison). Analyses are by Spang Microanalytical Laboratory.

2,6-Dibromoiodobenzene (1).[8] Since no modern detailed procedure for **1** is available, we describe our method here. To a solution of 2,6-dibromoaniline[9] (15 g, 0.06 mol) in 30 mL of concentrated HCl was added dropwise at 0–5 °C a solution of sodium nitrite (4.32 g, 0.062 mol) in 20 mL of water. After being stirred for 30 min, the diazonium solution was poured through a glass wool filter into a solution of potassium iodide (99.3 g) in 150 mL of water. The solution was stirred vigorously for 1 h, then 200 mL of CH_2Cl_2 and 20 mL of 1 N Na_2SO_3 were added successively. The aqueous layer was separated and washed with CH_2Cl_2, and the combined organic layers were washed with 10% aqueous NaOH and water and dried. The light-red solid residue obtained after solvent removal was washed with a little petroleum ether (35–60 °C) and recrystallized from benzene–ethanol to give 17 g (73%) of **1**, mp 98–99 °C (lit.[8] mp 99.0–99.5 °C).

General Procedure for *m*-Terphenyls (Table I). To a stirred arylmagnesium bromide solution (prepared from 17.5 mmol of aryl bromide and 19.3 mmol of magnesium in 40 mL of THF) under argon was added dropwise over 1 h at the temperature shown in Table I 5 mmol of 2,6-dibromoiodobenzene in 20 mL of THF. Stirring was continued for 3–10 h, after which the reaction was quenched with 40 mL of cold, dilute HCl. The THF was removed under reduced pressure and the aqueous solution was extracted several times with CH_2Cl_2. Combined organic layers were washed with Na_2SO_3 and water and dried. The residue obtained after solvent removal was chromatographed and/or recrystallized to give the products in the isolated yields shown in Table I.

It is not necessary to filter the excess magnesium from the aryl-Grignard reagent before use. The 2,6-dibromoiodobenzene can be added all at once instead of dropwise with only a modest exotherm, but the yield is decreased by about 10%.

Effect of Reactant Ratio on Yield. The reaction in entry 1, Table I, was studied briefly to determine the effect of phenylmagnesium bromide/**I** ratio on the yield of *m*-terphenyl. With the theoretical ratio of 3:1, the yield of **7** was 70%. This yield increased to 77% with a ratio of 3.5:1 as given in Table I and to 80–90% with a ratio of 5:1.

Effect of Other 1,2,3-Halobenzenes on Required Reaction Conditions. Limited studies were carried out with phenylmagnesium bromide and 1,2,3-trihalobenzenes other than **1**. 1,2,3-Tribromobenzene[15] and phenylmagnesium bromide gave a 61% yield of **7** after 15 h at room temperature or a 64% yield after 3.5 h at reflux. 2,6-Dichloroiodobenzene[8] gave a 53% yield of **7** after 24 h at room temperature.

Data for Compounds in Table I. 2,4,6,2″,4″,6″-Hexamethyl-1,1′:3′,1″-terphenyl (8): mp 133–134 °C; ^1H NMR δ 2.03 (s, 12 H), 2.31 (s, 6 H), 6.93–7.43 (m, 8 H); mass spectrum, *m/e* (relative intensity) 315 (25), 314 (100), 299 (26), 157 (33), 133 (28). Anal. Calcd for $C_{24}H_{26}$: C, 91.66; H, 8.33. Found: C, 91.87; H, 8.11. **1,1′:4′,1″:3″,1‴:4‴:1⁗-Quinquephenyl (9)**: mp 268–270 °C (lit.[11] mp 265–269 °C). **1,1′:3′,1″:3″,1‴:3‴,1⁗-Quinquephenyl (10)**: mp 113–115 °C (lit.[12] mp 117–117.5 °C). **4,4″-Dimethoxy-1,1′:3′,1″-terphenyl (11)**: mp 196–198 °C (lit.[13] mp 197–198 °C). **2,2″-Dimethoxy-1,1′:3′,1″-terphenyl (12)**: mp 97–98.5 °C; ^1H NMR δ 3.80 (s, 6 H), 6.96–7.69 (m, 12 H); mass spectrum, *m/e* (relative intensity) 290 (100), 260 (16), 231 (16), 215 (26), 131 (16), 119 (27), 115 (19), 101 (18), 94 (16). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.71; H, 6.33. **2,5,2″,5″-Tetramethoxy-1,1′:3′,1″-terphenyl (13)**: mp 122–124 °C; ^1H NMR δ 3.76 (s, 6 H), 3.79 (s, 6 H), 6.82–7.69 (m, 10 H); mass spectrum, *m/e* (relative intensity) 351 (23), 350 (100), 175 (21), 160 (34), 152 (35). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.40; H, 6.40. **1,1′-Bis(1,3-phenylene)naphthalene (14)**: mp 130–132 °C (lit.[14] mp 131–132 °C). **2,2′-Bis(1,3-phenylene)naphthalene (15)**: mp 145–146 °C (lit.[14] mp 143–144 °C).

2′-Iodo-1,1′:3′,1″-terphenyl (18). The general procedure was followed using **1** and phenylmagnesium bromide, but instead of quenching with dilute HCl, the reaction mixture was cooled in an ice bath and 1.5 equiv of iodine was added. The mixture was stirred vigorously as it warmed to room temperature. It was then washed with aqueous Na_2SO_3 and extracted several times with ether, and the combined ether extracts were washed with water and saturated NaCl solution and dried. The residue after removal of the solvent was chromatographed (silica gel, hexane) and recrystallized from ethanol to give **18** (88%), mp 113.5–115 °C (lit.[16] mp 114.4 °C).

1,1′:3′,1″-Terphenyl-2′-carboxanilide (19). From 1. The general procedure was followed with **1** (5 mmol) and phenylmagnesium bromide, but prior to aqueous quench, a solution of phenyl isocyanate (35 mmol) in 20 mL of THF was added to room temperature, and stirring was continued for 1 h. The mixture was poured into dilute HCl and extracted with CH_2Cl_2. The combined extracts were washed with water and dried, and the solvent was removed to leave a residue that was chromatographed on silica gel with petroleum ether–ethyl acetate (v/v, 70:30) as eluent. The product was recrystallized from acetic acid to give 1.1 g (63%) of pure **19**, mp 270–271 °C. **From 18.** The iodoterphenyl **18** was prepared as described above. To 356 mg (1 mmol) of **18** in 10 mL of THF at room temperature under argon was added ethylmagnesium bromide (1.15 mmol in 10 mL of THF), and the mixture was stirred for 6 h. The mixture was then heated at reflux for 30 min and cooled to room temperature, and phenyl isocyanate (1.6 mmol in 5 mL of THF) was added dropwise and stirring was continued overnight. Dilute HCl was added, and the mixture was extracted with ether. The combined extracts were dried and evaporated. The residue was chromatographed as above to give 296 mg (85%) of **19**, identical with that prepared above: ^1H NMR δ 6.85–7.59 (m); IR (KBr) 3230, 3190, 3130, 3060,

1645, 1605 cm^{-1}; mass spectrum, *m/e* (relative intensity) 349 (19), 257 (100), 228 (30). Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48. Found: C, 85.87; H, 5.54.

5′-Bromo-1,1′:3′,1″-terphenyl (21). The general procedure was followed, but with 2,4,6-tribromoiodobenzene (**20**)[17] in place of 1, and the mixture was heated at reflux for 1.5 h before quenching with aqueous HCl. The usual workup gave, after chromatography (silica gel, hexane eluent), 80% of **21** which was recrystallized from benzene–ethanol: mp 105–106 °C (107.5–109 °C after sublimation); ^1H NMR δ 7.46–7.50 (m, 7 H), 7.58–7.64 (m, 4 H), 7.70 (s, 2 H). Anal. Calcd for $C_{18}H_{13}Br$: C, 69.90; H, 4.20. Found: C, 69.71; H, 4.40.

(17) Hodgson, H. H.; Mahadevan, A. P. *J. Chem. Soc.* **1947**, 173.

Acknowledgment. We are indebted to the National Institutes of Health GM15997 for financial support of this research.

Registry No. **1**, 19821-80-8; **7**, 92-06-8; **8**, 103068-13-9; **9**, 3073-05-0; **10**, 16716-13-5; **11**, 1568-74-7; **12**, 103068-14-0; **13**, 103068-15-1; **14**, 103068-16-2; **15**, 103068-17-3; **18**, 82777-09-1; **19**, 103068-19-5; **20**, 21521-51-7; **21**, 103068-20-8; *p*-$C_6H_5C_6H_4MgBr$, 3315-91-1; *m*-$C_6H_5C_6H_4MgBr$, 103068-18-4; *o*-$CH_3OC_6H_4MgBr$, 16750-63-3; C_6H_5MgBr, 100-58-3; 2,4,6-$(CH_3)_3C_6H_2MgBr$, 2633-66-1; *p*-$CH_{30}C_6H_4MgBr$, 13139-86-1; 2,5-$(CH_3O)_2C_6H_4MgBr$, 62890-98-6; 2,6-$Br_2C_6H_3NH_2$, 608-30-0; 1,2,3-$(CH_3)3C_6H_3$, 608-21-9; 2,6-$Cl_2C_6H_3I$, 19230-28-5; 2,4,6-$Br_3C_6H_2I$, 21521-51-7; 1-naphthylmagnesium bromide, 703-55-9; 2-naphthylmagnesium bromide, 21473-01-8.

An Improved Method for S_N2-Type Demethoxycarbonylation of Activated Esters with 4-Aminothiophenol and a Cesium Catalyst

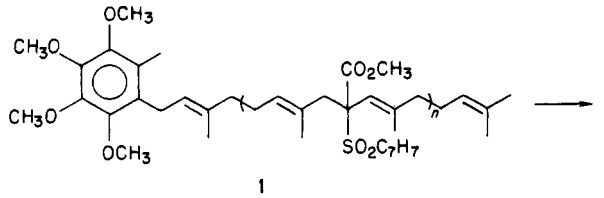
Ehud Keinan*† and Doron Eren

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel

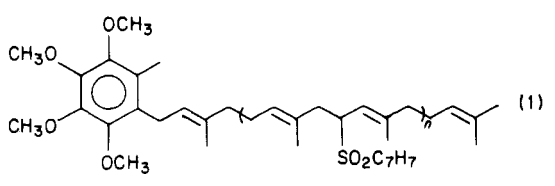
Received January 27, 1986

A powerful method for demethoxycarbonylation of activated methyl esters was developed, employing stoichiometric amounts of 4-aminothiophenol and catalytic quantities of cesium carbonate in hot (85 °C) DMF. The superiority of this technique over several other methods was demonstrated in a comparative study on linear polyprenoid substrates, in which the thiolate/Cs_2CO_3 approach benefited from shorter reaction times, lower temperatures, higher yields, and simpler workup procedures. The method enabled simultaneous removal of two methoxycarbonyl functions contained in a single molecule, a transformation representing a crucial step in the total synthesis of ubiquinone-10.

The synthesis of linear polyprenoid chains still represents a major challenge in synthetic organic chemistry,[1] particularly when compared to the fairly efficient oligomerization techniques that were developed for other important biopolymers and oligomers, including peptides, polynucleotides, and polysaccharides. We have recently developed a general route for making polyprenoids via a palladium(0)-catalyzed oligomerization of modified monoterpene unit.[2] One of the crucial steps in this approach involves the simultaneous removal of several methoxycarbonyl groups from a large molecule, as shown in the example in eq 1—one of the last steps in the total synthesis of ubiquinone-10.[3]



1



2 (1)

Demethoxycarbonylation at multiple reaction sites in a rather complex multifunctional molecule requires a highly efficient and yet chemoselective reaction that transforms each site in nearly quantitative yield while preserving all other functionalities.

Dealkoxycarbonylation of active esters via S_N2-type dealkylation[4] is certainly the most attractive one-step process for removal of the methyl ester entity, particularly when sterically hindered. The reaction usually involves heating of the substrate in a dipolar aprotic solvent in the presence of a nucleophile. Following Krapcho's original development of this approach,[5] which employed NaCl in dimethyl sulfoxide (Me_2SO), many other nucleophiles have been found applicable,[4] including halides, thiolates, *tert*-butoxide, thiocyanate, amines, and acetate. By far, the best method is probably that developed by Johnson[6] and modified by Trost and Verhoeven,[7] which employs tetramethylammonium acetate in hot (130 °C) Me_2SO or hex-

† Incumbent of The Joseph and Madeleine Nash Career Development Chair established by Fondacion Madelon, Zurich, Switzerland.

(1) (a) Britton, G. *Natl. Prod. Rep.* **1984**, *1*, 68. (b) Cainelli, G.; Cardillo, G. *Acc. Chem. Res.* **1981**, *14*, 89. (c) Isler, O.; Schudel, P. *Adv. Org. Chem.* **1973**, *4*, 115.

(2) (a) Keinan, E.; Eren, D., submitted for publication. (b) Keinan, E.; Eren, D. Israel Patent 71 482, 1985.

(3) For general information concerning ubiquinone-10, see: Yammamura, Y.; Folkers, K.; Ito, Y. *Biochemical and Clinical Aspects of Coenzyme Q_{10}*; Elsevier: Amsterdam, 1977(a), 1980(b), 1981(c), 1983(d); Vol. I(a), II(b), III(c), IV(d).

(4) (a) Krapcho, A. P. *Synthesis* **1982**, 805, 893. (b) McMurry, J. *Org. React. (N.Y.)* **1976**, *24*, 187. (c) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(5) (a) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *215*. (b) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(6) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188.

(7) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (c) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426.

0022-3263/86/1951-3165$01.50/0