groups and/or the rigid conformations may be detrimental to high biological activity.

Registry No. Benzo[*e*]pyrene diol epoxide **1**, 70981-75-8; benzo[*e*]pyrene diol epoxide **2**, 68151-05-3; triphenylene diol epoxide **1**, 70981-76-9; triphenylene diol epoxide **2**, 68151-06-4; *trans*-**1** benzo[*e*]pyrene tetraol, 70940-90-8; *cis*-**1** benzo[*e*]pyrene tetraol, 70981-77-0; *trans*-**2** benzo[*e*]pyrene tetraol, 70981-78-1; *cis*-**2** benzo[*e*]pyrene tetraol, 70981-79-2; *trans*-**1** triphenylene tetraol, 70940-91-9; *trans*-**2** triphenylene tetraol, 70981-80-5; *cis*-**2** triphenylene tetraol, 70981-81-6; benzo[*e*]pyrene 11-bromo-9,10,12-triol, major isomer, 70940-92-0; benzo[*e*]pyrene 11-bromo-9,10,12-triol, minor isomer, 70981-82-7; 10,11-epoxy-9,12-dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene, 70940-93-1; 10,11-epoxy-9,12-dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene diacetate, 70982-62-6; *trans*-**1** triphenylene tetraol tetraacetate, 70940-94-2; *trans*-**2** triphenylene tetraol tetraacetate, 70981-83-8; *cis*-**2** triphenylene tetraol tetraacetate, 70981-84-9; *trans*-**1** benzo[*e*]pyrene tetraol tetraacetate, 70940-95-3; *cis*-**1** benzo[*e*]pyrene tetraol tetraacetate, 70981-85-0; *trans*-**2** benzo[*e*]pyrene tetraol tetraacetate, 70981-86-1; *cis*-**2** benzo[*e*]pyrene tetraol tetraacetate, 70981-87-2.

Supplementary Material Available: Details on the hydrolysis of the benzo[*e*]pyrene and triphenylene diol epoxides to tetraols and their ^{1}H NMR spectra as tetraacetates, and the reaction of benzo[*e*]pyrene 9,10-dihydrodiol with *N*-bromoacetamide as well as the cyclization of the resultant bromo triols (4 pages). Ordering information is given on any current masthead page.

(16) A. W. Wood, W. Levin, D. R. Thakker, H. Yagi, R. L. Chang, D. E. Ryan, P. E. Thomas, P. M. Dansette, N. Whittaker, S. Turujman, R, E. Lehr, S. Kumar, D. M. Jerina, and A. H. Cooney, *J. Biol. Chem.*, **254**, 4408 (1979), and unpublished results of A. W. Wood.

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Removal of Benzyl-type Protecting Groups from Peptides by Catalytic Transfer Hydrogenation with Formic Acid

Summary: Formic acid is shown to be a particularly effective hydrogen donor for the rapid removal of peptide benzyl and benzyloxycarbonyl protecting groups by catalytic transfer hydrogenation.

Sir: Catalytic transfer hydrogenation has been shown to be a useful procedure for the removal of benzyl and benzyloxycarbonyl protecting groups in peptide synthesis.[1-4] Good yields of deprotected products have been obtained under relatively mild conditions using both cyclohexene and 1,4-cyclohexadiene as hydrogen donors. Transfer hydrogenation appears to be preferable in several respects to catalytic hydrogenation,[1-4] but has its own shortcomings. Probably the most important of these is the immiscibility of most peptides or peptide derivatives with the apolar hydrogen donors and/or their dehydrogenation product, benzene. The present work describes the use of formic acid, a good solvent for most peptides, as a convenient hydrogen donor for catalytic transfer hydrogenation.[5]

Results and Discussion

A large number of hydrogen donors have been used for catalytic transfer hydrogenation but cyclohexene has generally been preferred.[6] Rates of hydrogen transfer, however, vary considerably with different donors and the use of 1,4-cyclohexadiene, for example, greatly facilitates the deprotection of peptide benzyl and benzyloxycarbonyl derivatives and allows for more rapid deprotection at lower temperatures.[4] Formic acid, by the same criteria, appears to be a particularly facile hydrogen donor. Thus, N^{α}-(benzyloxycarbonyl)lysine in the presence of an equal weight of palladium black in 88% formic acid is completely deprotected in 30 s at room temperature.

Lower concentrations of formic acid in methanol also result in rapid removal of benzyl and benzyloxycarbonyl protecting groups but reduces the possibility of removal of acid labile protecting groups. Thus, as shown in Table I, 4.4% formic acid in methanol gives complete deprotection of both benzyl ester and benzyloxycarbonyl protecting groups in 5–10 min at room temperature. Under those conditions the *tert*-butyloxycarbonyl group appears to be quite stable as indicated by the 98% yield of (*tert*-butyloxycarbonyl)aspartic acid obtained from (*tert*-butyloxycarbonyl)aspartate β-benzyl ester (Table I). Thin layer chromatography of the product did not reveal the presence of any aspartic acid in the crude product.

The more refractory *N*-benzyl and nitro groups of N^{ϵ}-benzyllysine and nitroarginine are also removed under the same conditions but require approximately 10 and 5 h of reaction, respectively (Table I). Methionine-containing peptides give no particular difficulty. As shown in Table I, for example, the reaction with (benzyloxycarbonyl)-methionylglycine ethyl ester is complete in 10 min with a 92% yield. The reaction with *N*-(benzyloxycarbonyl)-*S*-benzylcysteinylphenylalanine ethyl ester, however, gave only a heterogenous mixture of products apparently due to incomplete reaction.

The results given in Table I demonstrate the feasibility of using formic acid as a hydrogen donor for the removal of *O*-benzyl, *N*-benzyl, and benzyloxycarbonyl protecting groups by catalytic transfer hydrogenation. The advantages of transfer hydrogenation over conventional hydrogenation have been described.[1-4] Formic acid, however, offers several additional advantages as compared to previously used hydrogen donors, and should be preferred in most cases. Thus, unlike cyclohexene or cyclohexadiene, formic acid is an excellent solvent for most peptides and peptide derivatives and therefore allows for complete solubilization of reactants and products in the great majority of cases. The reaction proceeds very rapidly at ambient temperature and pressure under relatively mild

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Table I. Catalytic Transfer Hydrogenation of Protected Amino Acids and Peptides with Formic Acid

starting material	product[a]	% yield[b]	reaction time[c]	mp, °C (reported)	TLC[d] solvent systems	TLC[d] starting materials	TLC[d] product
Z-Lys	Lys·formate	80	10 min	186-187	1	0.81	0.19
Z-Lys	Lys·formate	100[e]		186-187	1	0.81	0.19
Z-Gly-Gly	Gly-Gly·formate	90	10 min	207-211[f]	2	0.95	0
					3		0.33
Z-Phe-Phe·OEt	Phe-Phe-OEt·formate	97	10 min	252[f]	4	0.82	0
					5		0.82
Z-Gly-Arg(NO_2)	Gly-Arg·formate	86	5 h	115-118 (118-119)[g]	3	0.80	0.25
					6	0.73	0.14
Z-Lys(N^ϵ-Bzl)	Lys·formate	81	10 h	186-187	1	0.90	0.19
Boc-Asp(*O*-Bzl)	Boc-Asp	98	10 min	117-118 (118-119)[h]	2	0.94	0.94
Z-Met-Gly·OEt	Met-Gly-OEt·formate	92	10 min		7	0.91	0.05
Z-Cys(*S*-Bzl)-Phe-OEt	incomplete reaction				1	0.94	0.76

[a] A single product, chromatographically identical with authentic samples, was obtained in each case. [b] No attempt was made to optimize these yields. Reactions were run in a stirred reactor vessel except as noted. [c] Reaction times shorter than 10 min were not investigated. [d] Thin layer chromatography systems were as follows: 1, *n*-propanol/water, 70:30 on cellulose; 2, chloroform/methanol, 9:1 on cellulose; 3, 1-butanol/acetic acid/water, 4:1:5 on cellulose; 4, chloroform/methanol, 99:1 on silica gel G; 5, 1-butanol/acetic acid/water, 4:1:3 on silica gel G; 6, 1-propanol/9% ammonia, 4:1 on cellulose; 7, chloroform/methanol/20% ammonia, 9:1:0.15 on cellulose. [e] Using the column reactor. [f] Decomposes. [g] Determined for an authentic sample. [h] E. Schroder and E. Klieger, *Justus Liebigs Ann. Chem.* 673, 208 (1964).

conditions compatible with most other peptide protecting groups. All other products of the reaction are volatile.

Using palladium black or palladium on charcoal packed in a column rather than in a stirred reactor vessel allows for even more convenient reaction with minimal manipulation of sample and catalyst. Thus, benzyloxycarbonyl and *O*-benzyl protected peptides in 4.4% formic acid in methanol have been quantitatively deprotected by passage through a short (0.9 × 2 cm) loosely packed column of freshly prepared palladium black (~600 mg) in methanol. The deprotected peptide products are recovered after such a procedure by simple evaporation of the eluent and the column, after rinsing with a small additional volume of methanol, is ready for subsequent use with other samples. Small amounts of carbon dioxide produced during the reaction percolate up through the coarse, loosely packed catalyst and do not interfere with the reaction or with repeated use of such columns. The use of a column reactor eliminates the need to separate product from catalyst as a separate step after reaction, avoids most of the problems associated with filtering and handling of catalyst and sample, and can be easily incorporated into an automated system.[7]

Experimental Section. Formic acid (88%) was obtained from J. T. Baker Chemical Co. and methanol was a product of Mallinckrodt Chemicals. *N*-(Benzyloxycarbonyl)glycylglycine, N^α-(benzyloxycarbonyl)lysine, α-(benzyloxycarbonyl)methionylglycine ethyl ester, and palladium chloride were obtained from Sigma Chemical Co. Glycyl-L-arginine formate was obtained from Vega-Fox Biochemicals. N^α-(Benzyloxycarbonyl)-N^ϵ-benzyllysine was obtained from N^α-(benzyloxycarbonyl)lysine by the procedure of Benoiton.[8] (*tert*-Butyloxycarbonyl)aspartic acid β-benzyl ester and (benzyloxycarbonyl)glycylnitroarginine was prepared according to Polzhofer[9] and Riniker and Schwyzer,[10] respectively. (Benzyloxycarbonyl)-phenylalanylphenylalanine ethyl ester was prepared according to the procedure of Inouye et al.[11] (Benzyloxycarbonyl)-*S*-benzylcysteinylphenylalanine ethyl ester was prepared using the *p*-nitrophenyl ester method.[12] Palladium black was prepared according to the procedure of Wieland as described by Greenstein and Winitz.[13]

Procedure for Catalytic Transfer Hydrogenation in a Stirred Reactor. The protected peptide (~200 mg) dissolved in 2–10 mL of 4.4% formic acid–methanol was added to a 25-mL round-bottom flask containing approximately 200 mg of freshly prepared palladium black catalyst and 10 mL of 4.4% formic acid–methanol. The mixture was continuously stirred under a nitrogen atmosphere. A typical reaction was complete within 5 min as determined by thin layer chromatographic analysis of samples taken at various times. After 10 min, products were isolated by filtering off the catalyst and washing with an additional 10 mL of methanol followed by 10 mL of water. Longer reaction times, up to 10 h for the *N*-benzyl protecting group, were used as necessary until complete reaction was obtained. The combined filtrate plus methanol and water washes were then removed by evaporation under reduced pressure at room temperature. The products were crystallized from an appropriate solvent. To prevent breakdown of (*tert*-butyloxycarbonyl)aspartate during the workup, the filtrate plus methanol wash was diluted further with another 10 mL of water, partially evaporated at reduced pressure to about 5 mL, and then extracted into ethyl acetate. Evaporation of ethyl acetate left an oil which solidified upon standing.

Procedure for Catalytic Transfer Hydrogenation in a Column. A freshly prepared batch of coarse palladium black in methanol was poured into a short 0.9-cm chromatography column on top of a small plug of glass wool. In our experience a bed depth of about 2 cm of catalyst was sufficient for complete reaction on a single pass through the column. Samples of benzyloxycarbonyl peptides in 4.4% formic acid–methanol at about 5 mg/mL were placed on top of the bed of catalyst and allowed to flow slowly (~2 mL/min) through the column. A small

(7) In response to one of the reviewers comments we would like to point out that an inert atmosphere does not appear to be necessary and was not used with the column reactor. The same column has been used for at least 50 separate samples, in total amounting to more than 100 g of protected peptides.

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(12) M. Bodanszky, *Nature (London)*, **175**, 685 (1955).

(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol. 3, Wiley, New York, 1961, p 1233.

additional volume of formic acid–methanol was passed through the column to ensure complete removal of sample from the column. The combined eluent collected from the column was evaporated and products were isolated as described above. The column, after washing with methanol, is then ready for a subsequent sample. Bubbles of carbon dioxide that may adhere to the catalyst can be removed by sharp tapping on the side of the column and do not seem to interfere with the reaction. The same column can be used repeatedly.

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Registry No. Z-Lys, 2212-75-1; Z-Gly-Gly, 2566-19-0; Z-Phe-Phe-OEt, 5276-63-1; Z-Gly-Arg(NO_2), 35146-46-4; Z-Lys(N^{ϵ}-Bzl), 51021-86-4; Boc-Asp(*O*-Bzl), 7536-58-5; Z-Met-Gly-OEt, 27482-82-2; Z-Cys(*S*-Bzl)-Phe-OEt, 71171-87-4; Lys formate, 71171-88-5; Gly-Gly formate, 71171-89-6; Phe-Phe-OEt formate, 71171-90-9; Gly-Arg formate, 71171-91-0; Boc-Asp, 13726-67-5; Met-Gly-OEt formate, 71194-21-3; formic acid, 64-18-6.

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Reactions of Arylsulfonylacetylenes with Organolithium and Grignard Reagents: A New Synthesis of Acetylenes

Summary: α,β-Acetylenic sulfones react with organolithium and Grignard reagents to give a higher acetylene and a sulfinate salt. The process corresponds to nucleophilic substitution by the organometallic for the arylsulfonyl group.

Sir: The reaction of α,β-acetylenic sulfones with nucleophiles in a protic environment[1,2] and with organocopper reagents in an aprotic medium[3] results in products of addition to the triple bond. We wish to report our preliminary results concerning the reaction of α,β-acetylenic sulfones with organolithium and Grignard reagents to give products of substitution rather than addition.[4] Similar results have recently been reported with vinyl sulfones.[5,6]

Alkyl- and aryllithium reagents react rapidly and cleanly with arylsulfonylacetylenes to yield products of substitution (Table I). Alkyl Grignard reagents also give products of substitution in good to excellent yields (Table II).

$$ArSO_2C{\equiv}CR + R'M \rightarrow R'C{\equiv}CR + ArSO_2M \quad (1)$$

The reaction of organolithium reagents with α,β-acetylenic sulfones is rapid and complete in less than 1 min, even at −78 °C. Grignard reagents, on the other hand, required 12–24 h at room temperature to react completely. In general, yields are higher and cleaner with organolithium reagents. This reaction sequence represents a new synthesis of acetylenes,[7] including di-*tert*-butylacetylene (Table I, entry 6), from the appropriate α,β-acetylenic sulfone (readily available as by the addition of the sulfonyl iodide to the acetylene and subsequent dehydroiodination).[8]

Table I. Reactions with Organolithium Reagents[a,e]

Ar	R	R′	% yield[b]
C_6H_5	C_6H_5	n-C_4H_9	98
mesityl	C_6H_5	t-C_4H_9	60
mesityl	C_6H_5	C_6H_5	81
mesityl	C_6H_5	p-$CH_3{\cdot}C_6H_4$	75
p-$CH_3C_6H_4$	t-C_4H_9	n-C_4H_9	84
p-$CH_3C_6H_4$	t-C_4H_9	t-C_4H_9	95
C_6H_5	H	C_6H_5	61[c,d]

[a] All reactions were carried out in THF as solvent. [b] Yields are actual isolated yields. [c] Yield based on VPC analysis. [d] Two equivalents of organolithium were used. [e] Products were characterized by nuclear, IR, and mass spectroscopic data.

Table II. Reactions with Grignard Reagents[a,d]

Ar	R	R′	% yield[b,c]
mesityl	C_6H_5	n-C_4H_9	75
mesityl	C_6H_5	C_2H_5	87
mesityl	C_6H_5	s-C_3H_7	91
C_6H_5	C_6H_5	C_6H_5	52
C_6H_5	C_6H_5	PhC≡C	24
C_6H_5	C_6H_5	p-$CH_3C_6H_4S$	29

[a] All reactions were carried out in THF as solvent. [b] Yields are actual isolated yields. [c] All products were purified by column chromatography. [d] Products were characterized by nuclear, IR, and mass spectroscopic data.

The reaction is believed to involve initial attachment of the organometallic to the sulfonyl-bearing (α) carbon (presumably facilitated by prior complexation of the organometallic to the sulfonyl oxygens), followed by expulsion of the arylsulfinate leaving group. Additional work on the reaction mechanism and into the scope and limitations[9] of the reaction are continuing in this laboratory. The following procedures are representative.

General Procedure for the Preparation of Alkynes by Treating Arylsulfonylacetylenes with Organolithiums. The reaction was carried out in a 100-mL three-neck flask equipped with a nitrogen inlet tube, rubber stopper, and Teflon magnetic stirring bar. The glassware was assembled cold, flame dried, and allowed to cool in a stream of nitrogen. The sulfone (7–10 mmol) was added to the cooled apparatus. THF (20–30 mL, previously dried over sodium turnings and freshly distilled) was added via syringe and the sulfone was brought into solution by the stirrer. The solution was cooled to −74 °C with a dry ice–acetone bath and an equimolar amount of the organolithium reagent was added via syringe. The rate of addition was usually 1 mL/min, although the rate of addition seems to have no effect on either product outcome or percent yields. Twenty minutes after the last of the organolithium reagent was added, the solution was removed from the dry ice–acetone bath and allowed to warm to room temperature. Upon warming, the solution usually turned from a dark red or dark green to an amber color.

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(9) Preliminary indications are that acetylenes bearing at least one propargylic-type hydrogen suffer from complications (possibly isomerizations to the corresponding allenes, etc.) which may limit the general utility of this approach to higher acetylenes.

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