A Simple and Economical Synthetic Route to *p*-Ethynylaniline and Ethynyl-Terminated Substrates

Anastasios P. Melissaris† and Morton H. Litt*

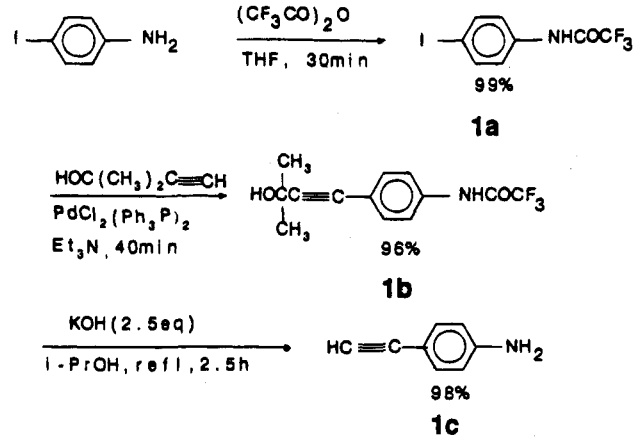
Department of Macromolecular Science, Case Western Reserve University, Cleveland, Ohio 44106

Received July 12, 1993 (Revised Manuscript Received June 20, 1994)

Introduction

Acetylenic compounds have been used for the synthesis of high performance polymers and for systems which exhibit nonlinear optical properties. Classical methods for the synthesis of terminal arylacetylenes in general involve manipulation of preformed, two-carbon side chains and include methods such as the Vilsmeier method[1-3] or the halogenation–dehydrohalogenation sequence of vinyl aromatics[4] and ketones.[5,6] An innovation in the synthesis of arylacetylenic compounds has been to use protecting groups.[7] Acetylene, protected at one end, can be added to an aromatic nucleus via coupling at the free end. Subsequent removal of the protecting group generates a terminal arylacetylene. The widely accepted procedure for the addition of an acetylenic substituent to an aromatic nucleus is the Stephens–Castro coupling reaction[8-10] between an aryl iodide and a protected acetylide in pyridine at reflux. More recent advances in the synthesis of arylacetylenes[11,12] use a two-step route; the first step involves the coupling of an aryl iodide with (trimethylsilyl)acetylene (TMSA) in the presence of Pd(0)/Cu(I) in pyridine. The second step is removal of the protecting group (trimethylsilyl) to yield the arylacetylene. The trimethylsilyl protecting group is easily removed by treatment with dilute potassium hydroxide or potassium carbonate. However, because of the prohibitively high cost of the TMSA, this route has been limited to small-scale preparations. There has been a great interest in the development of methods for introducing an ethynyl group[13-18] into organic structures.

Scheme 1. Synthetic Route to *p*-Ethynylaniline



For the synthesis of *p*-ethynylaniline (**1c**) (Scheme 1), four methods[13,15-18] have been reported. The yields vary from poor to moderate (30–65%) and the reactions are cumbersome and costly to perform on a large scale. The most interesting procedure for the synthesis of **1c**[11] entails coupling of *p*-iodoaniline with (trimethylsilyl)-acetylene (TMSA) in the presence of a palladium complex and a copper(I) salt. Due to the high cost of TMSA, this route for all practical purposes has been limited to small-scale procedures.[19-23] J. Stille and T. Takeichi[17] synthesized **1c** using (tributylstannyl)acetylene (TBSA) and *p*-iodoaniline in 30% overall yield.

Attempts to synthesize larger quantities of **1c** using inexpensive reagents have been unsuccessful up to date. 2-Methyl-3-butyn-2-ol (MEBYNOL) has been used by other investigators to synthesize **1c** because of its very low cost. Bardamova et al.[15] synthesized **1c** on a milligram scale by direct coupling of *p*-iodoaniline with MEBYNOL, followed by deprotection and heating the intermediate 4-anilino-2-methyl-3-butyn-2-ol under a high vacuum in the presence of well-ground KOH and catalytic amounts of hydroquinone. However, most of the desired product decomposed under these severe conditions. Takalo et al.[16] reported a modified procedure for deprotecting 4-anilino-2-methyl-3-butyn-2-ol, heating under distillation conditions in the presence of NaOH pellets in toluene for 2 h. **1c** was synthesized in 30% overall yield. The methods of Bardamova[15] and Takalo[16] have not been used for the synthesis of **1c** because the yields were low and some decomposition products were generated during the deprotection step.

Due to the high cost of TMSA, we decided to develop a simple high yield route to **1c** using the very inexpensive reagent MEBYNOL. We have reported a new synthesis of *p*-ethynylbenzoic acid and p-ethynyl benzoyl chloride, using MEBYNOL.[14] We now report an economical and efficient synthesis of **1c** using a modified route which is simpler and less expensive than the methods previously reported. This method gives an almost quantitative yield of high purity product. The low yields and the various

† Current address: Materials Engineering Division, Research Institute, University of Dayton, Dayton, OH 45469.

(1) Staab, H.; Neunhoffer, K. *Synthesis* **1974**, 424.
(2) Rosenblum, M.; Brawn, N.; Papenmeir, J.; Applebaum, M. *J. Organomet. Chem.* **1966**, *6*, 173.
(3) Boschan, R. Hughes Aircraft Co. Private communication cited in ref 12.
(4) Collier, W.; Macomber, R. *J. Org. Chem.* **1973**, *38*, 1367.
(5) Kocienski, P. *J. Org. Chem.* **1974**, *39*, 3285.
(6) Bartlett, P.; Rosen, L. *J. Am. Chem. Soc.* **1942**, *64*, 543.
(7) Walton, D. In *Protective Groups in Organic Chemistry*; McOmie, J., Ed.; Plenum Press: London, 1973; Chapter 1.
(8) Castro, C.; Stephens, R. *J. Org. Chem.* **1963**, *28*, 2163.
(9) Stephens, R.; Castro, C. *J. Org. Chem.* **1963**, *28*, 3313.
(10) Castro, C.; Havlin, R.; Honwad, V.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.
(11) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagirara, N. *Synthesis*, **1980**, 627.
(12) Austin, W.; Billow, N.; Kelleghan, W.; Lau, K. *J. Org. Chem.* **1981**, *46*, 2280.
(13) Sabourin, E; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 5135.
(14) Melissaris, A; Litt, M. *J. Org. Chem.* **1992**, *57*, 6998.
(15) Bardamova, M; Trotsenko, Z; Kotlyareskii, I. *Bull. Akad. Science USSR, Div. Chem.* **1982**, 1057.
(16) Takalo, H; Kankare, J; Hanninen, E. *Acta Chem. Scand.* **1988**, *B*(42), 448.
(17) Takeichi, T; Stille, J. *Macromolecules* **1986**, *19*, 2093.
(18) Fujiwara, H; Kihara, K. Japanese Patent 03 38 551, 1991; *Chem. Abstr.* **1991**, *115*, 49061c.
(19) Abraham, T; Soloski, E; Benner, C. L; Evers, R. C. *Report* 1989, *WRDC-TR-89-4115*, **1990**, *90*(12); *Chem. Abstr.* **1991**, *115*, 9379f.
(20) Yuan, Z; Taylor, N. J; Marder, T. B; Williams, I. D; Kurtz, S. K; Cheng, L. T. *J. Chem. Soc., Chem. Commun.* **1990**, 1489.
(21) Schering, A. G. Ger. Offen. DE 3 816 062, 1989; *Chem. Abstr.* **1990**, *113*, 40667f.
(22) Choe, E. W. U.S. Patent 4,703,096, 1987; *Chem. Abstr.* **1988**, *108*, 76103e.
(23) Graham, E. M; Miskowski, V. M.; et al. *J. Am. Chem. Soc.* **1989**, *111*(24), 8771.

0022-3263/94/1959-5818$04.50/0

melting points of **1c** found using Bardamova's[15] and Takalo's[16] methods were due to the sensitivity of the amino group under their experimental conditions. We realized that an effective blocking group for the amino group and a strongly basic medium for the deprotection reaction were needed. The blocking group should be of low cost, should give a high yield of the protected anilino derivative, and should be easily removed.

The trifluoroacetyl group fulfills the above requirements. The ease with which this group can be introduced, and more importantly, the facility with which it can be removed makes it highly attractive for protecting *p*-iodoaniline. The system, 2-propanol or 2-butanol/KOH, used for the synthesis of *p*-ethynylbenzoic acid[14] should be very effective because the intermediate 4-(*N*-(trifluoroacetyl)anilin-4-yl)-2-methyl-3-butyn-2-ol (**1b**), the base KOH, and **1c** should be soluble in the alcohols. Because of the low boiling point of the system, the final product, **1c**, should neither decompose nor polymerize during the deprotection step.

We took advantage of the sensitivity of the trifluoroacetamido linkage toward potassium or sodium hydroxide by carrying out the cleavage of the 2-hydroxypropyl and trifluoroacetamido group in *i*-PrOH or 2-butanol in order to prepare **1c** in high yield and high purity.

MEBYNOL has not been used for large scale syntheses of arylacetylenes even though it is much less expensive than TMSA; it has been limited to small scale preparations.[24-27] This is because the 2-hydroxypropyl group is not easily removed when the benzene ring has electron donating substituents. Thus, after the formation of the 4-aryl-2-methyl-3-butyn-2-ol-4-yl adduct, the next step, which involves the removing of the protecting group (2-hydroxylpropyl) as acetone, appeared to be complicated. Severe reaction conditions were needed, such as strong alkaline environment and high temperatures for the deprotection reaction to go to completion. During the deprotection step, byproducts appeared or side reactions took place if base-sensitive groups were present in the molecule. Another objective of this work was to generalize the deprotection procedure to other bisbutynol substrates; thus, the deprotection of ethynyl-substituted benzyl ethers on a large scale by this procedure was studied.

Results and Discussion

N-(Trifluoroacetyl)-4-iodoaniline (**1a**), was prepared by reacting *p*-iodoaniline with an excess of trifluoroacetic anhydride in THF. The reaction is very exothermic and is over in 20 min. The solvent was evaporated and the light tan residue was stirred with H_2O in order to remove all remaining trifluoroacetic acid. **1a** was prepared in 99% yield and 99% purity (HPLC). **1a** has been previously synthesized in 35% yield by iodination[28] of (trifluoroacetamido)aniline. In the second step, **1a** was coupled with 2-methyl-3-butyn-2-ol (MEBYNOL) in deaerated and dried Et_3N using Pd(0)/CuI catalysis to give the intermediate 4-(*N*-(trifluoroacetyl)anilin-4-yl)-2-methyl-3-butyn-2-ol (**1b**) with 99% purity (HPLC) and 99% conversion. This reaction was completed in less than 30 min. The solvent was evaporated and the resulting brown sticky mass which contained Et_3N in a molar ratio, **1b**/Et_3N = 1/1.1, respectively, was recrystallized from a small volume of toluene. **1b** was obtained as an off-white crystalline product in 90% yield. Even though the conversion was 99%, only the 90% of **1b** was isolated by the recrystallization. The trapped Et_3N could not be removed by vacuum evaporation even at 80 °C. This is probably because the proton of trifluoroacetamido group is relatively acidic and interacts strongly with Et_3N (hydrogen bonding). Following this hypothesis, the brown sticky mass was stirred with glacial acetic acid and crystalline **1b** was obtained in 96% yield.

In a single, simple step **1b** was hydrolyzed and deprotected by being refluxed in *i*-PrOH or 2-BuOH for 2.5 h, using an excess of potassium hydroxide. After evaporating the solvent, redissolving in CH_2Cl_2, and filtering the residue through a very short column of silica gel in a cold room (5–8 °C), *p*-ethynylaniline (**1c**) was obtained in 98% yield and 99% purity as a pale yellow crystalline material. When the flash chromatography was done at rt, **1c** was isolated in 90% yield, possibly due to some hydrolysis (formation of acetophenone derivative) or self-polymerization. Upon standing at rt, crystalline **1c** changes color from pale yellow to dark yellow and then to tan or brown, which means that it polymerizes slowly. **1c** can be stored safely at −20 °C.

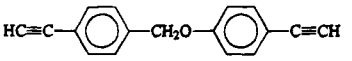
The success of the present method can be attributed to the following factors. First, the trifluoroacetyl group as a blocking agent not only protects the amino group from side reactions but also strongly activates (strong electron withdrawing group) the carbon para to the acetamidogroup during the coupling reaction. The second factor is the very effective basic medium used for the deprotection reaction. The same system (*i*-PrOH/KOH) has been successfully used for the synthesis of *p*-ethynylbenzoic acid.[14]

The present method has several advantages over that of Takahashi's[11] because: (1) MEBYNOL was used as a coupling agent in place of the expensive (trimethylsilyl)-acetylene, (2) a much higher overall yield was obtained, 93 instead of 65%, and (3) this reaction could be run with high yields even when using large quantities of reagents.

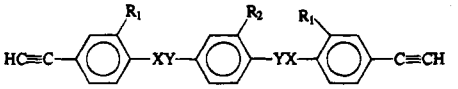
To generalize the use of the alcohol/base system for deprotecting different types of bisbutynol adducts, bis-(4-aryl--2-hydroxy-2-methyl-3-butyn-4-yl) benzyl ethers (BBBE) synthesized in our laboratory[29] were deprotected to yield their corresponding bis(*p*-ethynyl)benzyl ethers, Chart 1. For the deprotection of BBBE, literature procedures were applied without any success. The procedure of Marvel and Trumbo[24] for the synthesis of 1,3-diethynylbenzene was attempted without success. (The bisbutynol adduct in dry toluene/methanol/KOH was heated in a 120 °C bath for 3–4 h and the evolved acetone was distilled off periodically.) The failure of this reaction was attributed to the low solubility of the base in this mixed solvent and the fact that the mixed solvent did not have a high enough boiling point to activate the system. Attempts were made to deprotect the bisbutynol adducts by following the method of Onopchenko et al.[26] using refluxing toluene containing a catalytic amount of sodium hydroxide pellets. Cleavage was incomplete and a mixture of compounds was obtained. This failure was

(24) Trumbo, D.; Marvel, C. S. *J. Polym. Sci. Part A: Polym. Chem. Ed.* **1986**, *24*, 2311.
(25) Seto, K.; Shimojitosho, H. *Japanese Patent* 01 261 353; *Chem. Abstr.* **1990**, *112*, 197858w.
(26) Onopchenko, A.; Sabourin, E.; Selwitz, C. *J. Org. Chem.* **1979**, *44*, 1233.
(27) Harris, F.; Pamidikulala, A.; Gupta, R.; Das, S.; Wu, T.; Mock, G. *J. Macromol. Sci.-Chem.* **1984**, *A21*, 1117.
(28) Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552.
(29) Melissaris A. P.; Litt, M. H. *Macromolecules* **1994**, *27*, 883.

Chart 1. Chemical Structures of 2–7



2



Compound	X	Y	R_1	R_2
3	O	CH_2	H	H
4	O	CH_2	Cl	H
5	CH_2	O	H	CH_3
6	CH_2	O	H	Cl
7	CH_2	O	H	H

attributed to the fact that the bisbutynol adducts of **2–7** needed more severe conditions for deprotection because of the electron donating benzylic and phenolic groups.

Since we wanted to prepare large quantities of the monomers, an attempt was made to develop a general and inexpensive procedure which could be applied to the whole series of bisbutynol substituted benzyl ethers. A variety of combinations of bases and solvents or mixed solvents were studied to determine optimum reaction conditions. For example, the adduct of **4** was successfully deprotected within 4 min by heating 1 equiv of the intermediate in dried DMF containing *t*-BuOK (2 equiv). However this system did not work well for the other intermediates. The adduct of **2** was deprotected within 15 min in refluxing toluene containing *t*-BuOK; this system was not suitable for the deprotection of the other adducts because byproducts formed after 5 min of heating. The best system developed was NaOH/1-BuOH because (1) it is inexpensive, (2) it could be applied to all bisbutynol adducts, (3) the high boiling point of the 1-butanol reduced the reaction time to less than 1 h (much less than procedures previously reported[24,27]), and (4) NaOH has high solubility in refluxing 1-BuOH. This system appears to be much more effective than others which have been used for the deprotection of monobutynol adducts,[26] It should be noted that the formation of the monobutynol monoethynyl adduct took place within 4 min (checked by HPLC) but the reaction was complete only after 1 h. Although 2-propanol was successfully used as solvent in the deprotection of an arylbutynol adduct bearing an electron withdrawing group,[14] the deprotection did not go to completion for these materials (90% deprotection), even after being refluxed for 3 h. The purity of EBEs was checked with HPLC and GPC and ranged from 96 to 99%. No attempt was made to further purify them by recrystallization or column chromatography. The physical characteristics of EBEs **2–7** shown in Chart 1 are given in Table 1. Full characterization data are reported in the paper on the synthesis of the EBE's.[29]

Experimental Section

Materials and Methods. The purification methods for the reagents and the techniques used in this work have been reported elsewhere.[14,29] Bis(4-aryl-2-hydroxy-2-methyl-3-butyn-4-yl) benzyl ethers, BBBE, have been synthesized in our laboratory and published elsewhere.[29]

Table 1. Physical Characteristics for 2–7

compd	yield (%)	T_{melt}[a] (°C)	HPLC, t_R (min)
2	90	98	2.80
3	99	164	3.06
4	92	138	3.37
5	96	94	3.34
6	92	125	3.00
7	94	197	2.87

[a] Defined by DSC (15 °C/min under N_2).

***N*-(Trifluoroacetyl)-4-iodoaniline (1a).** *p*-Iodoaniline (109.5 g, 0.5 mol) was dissolved in dried THF (0.5 L). Trifluoroacetic anhydride (210 g, 1 mol) was added portionwise to the solution at 0–2 °C within 15 min. The solution was further stirred for 40 min at rt. It was evaporated to dryness and the resulting light tan crystalline residue was stirred with 1.2 L of H_2O (twice). It was filtered and dried at 50 °C under vacuum, affording **1** as off-white flakes (157.2 g, yield = 99%) with mp 141–142 °C (lit. mp[28] 142 °C) and 99.5% purity: HPLC (methanol as eluent, pressure 1700 psi, and a flow rate of 0.8 mL/min) showed a single peak with retention time t_R = 3.18 min; ^{1}H NMR (200 MHz, acetone-d_6) δ 7.57(d, J = 8.6 Hz, 2H, aromatic ortho to -NHCOCF$_3$), 7.74 (d, J = 8.7 Hz, 2H, aromatic ortho to -I), 7.8 (bs, 1H, -NHCO-).

4-(*N*-(Trifluoroacetyl)anilin-4-yl)-2-methyl-3-butyn-2-ol (1b). Dichlorobis(triphenylphosphine)palladium (0.83 g, 1.18 mmol) was added under N_2 to a solution of Ph_3P (3.14 g, 12 mmol), CuI (0.83 g, 4.36 mmol), **1** (157.2 g, 0.5 mol), and MEBYNOL (106.7 g, 1.27 mol) in 1.5 L of dry Et_3N, and the mixture was stirred at 50 °C for 20 min and then refluxed for 20 min. The mixture was cooled to rt, and 0.75 L of diethyl ether was added. Triethylamine hydroiodide precipitated quantitatively. The mixture was filtered and the precipitate was washed with diethyl ether (150 mL). The dried salt weighed 113.3 g (0.49 mol) which corresponds to 99% conversion. The combined filtrates were evaporated under reduced pressure. A brown sticky mass was obtained which contained Et_3N in a molar ratio **1b**/Et_3N = 1/1.1. Crystalline **1b** was obtained by two procedures: (1) The brown sticky mass was recrystallized from toluene (120 mL). A light tan crystalline product was obtained which was dissolved in CH_2Cl_2 (3.8 L) and extracted three times with H_2O (1 L per time). The organic layer was dried with $MgSO_4$ and filtered. The filtrate was evaporated to dryness and **1b** was obtained as a light tan colored product (121.3 g, yield = 90%) with mp 135–136 °C and 99% purity: HPLC (MeOH as eluent, pressure 2000 psi and a flow rate of 0.7 mL/min) showed a single peak with retention time t_R = 2.33 min; ^{1}H NMR (200 MHz, $CDCl_3$) **1b** δ 1.58 (s, 6H, -CH$_3$), 4.55 (s, 1H, -OH), 7.32 (d, 2H, J = 8.6 Hz, aromatic ortho to acetylenic bond), 7.65 (d, 2H, J = 8.6 Hz, aromatic ortho to trifluoroacetamido group), 10.64 (s, 1H, -NHCO- of trifluoroacetamido group). (2) In a second run, the brown sticky mass was stirred with glacial acetic acid (80 mL) for 10 min at 5 °C and for a further 50 min at rt. The solvent was evaporated and the viscous dark orange residue was stirred with 1.3 L of H_2O twice. **1b** was isolated as a light tan crystalline product (130.1 g) in 96% yield and mp 134–135 °C. Its ^{1}H NMR spectral data were the same as above.

4-Ethynyl Aniline (1c). Seventy and one-half grams (1.26 mol) of KOH were dissolved in refluxing *i*-PrOH (1.5 L), and 121.3 g (0.45 mol) of **1b** was added at once. The solution was refluxed for 2.5 h and then evaporated to dryness at 40–45 °C. The resulting residue was stirred with cold hexanes (80 mL) to remove traces of *i*-PrOH. The mixture was filtered and the tan residue was washed again with cold hexanes (40 mL). The product as a suspension in CH_2Cl_2 was placed at the top of a column of silica gel (125 g) with an effective height of 29 cm at 5–8 °C. CH_2Cl_2 was used as solvent for the packing of the column. The system was eluted with CH_2Cl_2 (1.7 L) until the eluent was colorless. The light yellow filtrate was evaporated under reduced pressure. **1c** was obtained as a pale yellow crystalline product (51.3 g, yield = 98%) with mp 104–105 °C (lit. mp[11] 104–105 °C, lit. mp[15] 101–102 °C, lit. mp[16] 99.5–101 °C) and 99% purity: HPLC (MeOH as eluent, pressure 2000 psi and a flow rate of 0.8 mL/min) showed one single peak with retention time t_R = 2.51 min (99% purity); ^{1}H NMR (200 MHz, $CDCl_3$) **1c** δ = 2.96 (s, 1H, acetylenic), 3.79 (bs, 2H, -NH$_2$), 6.56 (d, 2H, J = 8.55 Hz, aromatic ortho to -NH$_2$), 7.25 (d, 2H, J =

8.55 Hz, aromatic ortho to acetylenic group). When the chromatography was carried out at rt, 4-ethynylaniline was isolated in 90% yield. This is possibly due to hydrolysis with the formation of an acetophenone derivative or self-polymerization. Similar yields were obtained when *i*-BuOH was used in place of *i*-PrOH. It should be noted that if a yellow semicrystalline instead of a crystalline product is obtained from the column chromatography, this is due to incomplete evaporation of the deprotection solvent. This semicrystalline product should be stirred with CH_2Cl_2 (10–15 mL) for 2 h at rt. The mixture can then be filtered and the residue rinsed with cold CH_2Cl_2 and dried at 30–35 °C under vacuum to yield a crystalline pale yellow product.

Deprotection of Bis(4-aryl-2-hydroxy-2-methyl-3-butyn-4-yl) Benzyl Ethers To Yield 2–7. The deprotection procedure for the bisbutynol adduct of **3** is detailed below as representative of the reaction conditions. To a 2.5 L single-neck flask equipped with condenser were added the bisbutynol adduct of **3** (50 g, 110 mmol) and 1-butanol (1 L). The solution was heated to reflux and sodium hydroxide (18 g, 450 mmol) was added at once. The mixture was heated at reflux for 1 h. The solvent was rotoevaporated and the residue was stirred with 2 L of H_2O three times and filtered. Upon drying under vacuum at 45 °C, light tan flakes of crystalline solid **3** were obtained (37.1 g, yield = 99%) with 99.5% purity. **2** and **4–7** were obtained in 90–96% yield and 96–99% purity (HPLC and GPC). Their physical data are listed in Table 1. Full characterization data are reported in Melissaris and Litt.[29]

Conclusions

A simple and economical synthesis of *p*-ethynylaniline in 93% overall yield on up to a 0.5 mol scale is reported. This route gives an almost quantitative yield of high purity product. It is less expensive, faster, and gives much higher yields than the methods previously reported.

The deprotection procedure was expanded to bis(4-aryl-2-hydroxy-2-methyl-3-butyn-4-yl) benzyl ethers; they were successfully deprotected to yield *p*-ethynylbenzyl ethers in high yield and purity. For this deprotection reaction, many combinations of bases and solvents were studied to optimize the reaction conditions. The system NaOH/1-BuOH appears to be the most attractive one for the deprotection of benzyl ethers because (1) it is inexpensive, (2) it could be applied to all bisbutynol adducts, (3) sodium hydroxide exhibited high solubility in the refluxing 1-butanol, and (4) the high boiling point of 1-butanol decreased the reaction time required for deprotection to less than 1 h.

In general, the use of KOH or NaOH in primary or secondary alcohol solvent has been found to be an excellent deprotection method. The particular alcohol used determines the reaction rate. 2-Propanol works well with active compounds. Higher boiling alcohols are needed if the intermediates have electron donating substituents which stabilize them. The new deprotection procedure was found to be very effective when compared to those reported in the literature.

Acknowledgment. Financial support by Edison Polymer Innovation Corporation (EPIC) is gratefully acknowledged.