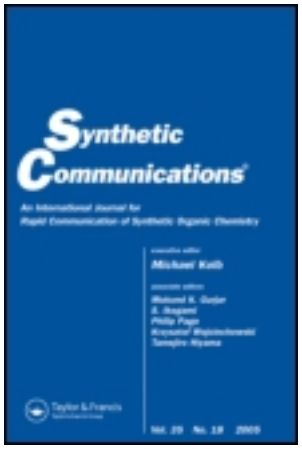

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K_3PO_4-KOH Mixture as Efficient Reagent for the Deprotection of 4-Aryl-2-methyl-3-butyn-2-ols to Terminal Acetylenes

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K_3PO_4–KOH MIXTURE AS EFFICIENT REAGENT FOR THE DEPROTECTION OF 4-ARYL-2-METHYL-3-BUTYN-2-OLS TO TERMINAL ACETYLENES

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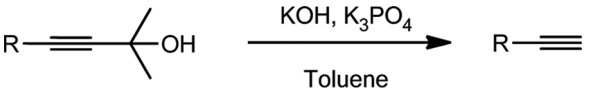
GRAPHICAL ABSTRACT



18 examples, 70 - 99% yield

Abstract *A mixture of potassium hydroxide and potassium phosphate was found to be an active reagent mixture for the cleavage of 2-hydroxypropyl-protected acetylenes. The reaction was performed in toluene at reflux temperature and gave terminal acetylenes in good to excellent yields within very short periods of time. Numerous other functional groups are tolerated.*

Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for full experimental and spectral details.*

Keywords Acetylenes; deprotection; synthesis

INTRODUCTION

Terminal arylacetylenes are key building blocks for the construction of a variety of organic compounds including natural products,[1] materials for organic light-emitting diodes (OLEDs),[2] and organic photovoltaic cells (OPVCs).[3] They are also interesting starting materials for the synthesis of pharmacologically active heterocycles.[4]

The palladium-catalyzed Sonogashira–Hagihara cross-coupling of aryl halides with mono-protected acetylenes followed by removal of the protecting group is an important synthetic approach to terminal acetylenes and their derivatives. The most commonly used mono-protected acetylenes are trimethylsilylacetylenes (TMSA), triisopropylsilylacetylenes (TIPSA), and 2-methyl-3-butyn-2-ols (MEBYNOL). An

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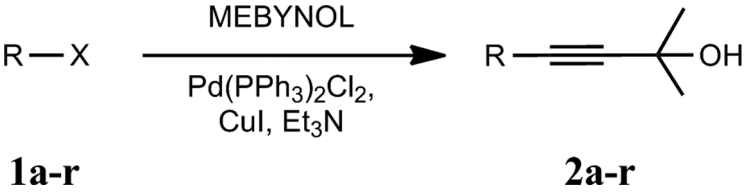
advantage of the trialkylsilylacetylenes is simple deprotection by treatment with bases or fluoride at ambient temperature.[5] A disadvantage of TMSA and TIPSA, however, is the higher price in comparison to 2-methyl-3-butyn-2-ol. MEBYNOLs usually undergo smooth coupling reactions with aromatic systems in excellent yields,[6] and the purification of the reaction products is very simple and efficient because of the considerably different polarities of starting materials and products.[1,7] Nevertheless, the removal of the 2-hydroxyisopropyl group of the protected acetylenes requires harsh conditions. Usually, strong bases (KOH, NaOH, NaH, etc.) in combination with high temperatures (such as reflux temperature in *n*-BuOH[8]) and long reactions times (up to 5 h, vide infra) are applied. These factors often lead to undesired side reactions and decreased yields of the products.

In continuation of our interest in cross-coupling reactions catalyzed by N-heterocyclic carbene complexed transition metals,[9] heterocyclic synthesis,[10] and metal-organic frameworks,[11] we required a variety of terminal acetylenes and therefore tried to improve known deprotection procedures. Here we describe a very efficient and simple method for the deprotection of 4-aryl-2-methyl-3-butyn-2-ols to terminal acetylenes. The desired products are obtained in good to excellent yields, most of them within a few minutes.

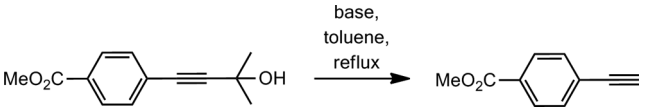
DISCUSSION

4-Aryl-2-methyl-3-butyn-2-ols were prepared by Sonogashira–Hagihara cross-coupling from aryl/heteroaryl halides, MEBYNOL, and a $Pd(PPh_3)_2Cl_2$–CuI mixture as catalyst as described before.[1,6,7] The reaction was monitored by thin-layer chromatography (TLC; Scheme 1).

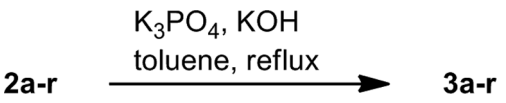
We choose methyl 4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzoate as the model compound for screening different bases for the deprotection (Scheme 2). Potassium phosphate[6d] and potassium carbonate[7a] proved to be totally ineffective (Table 1, entries 1 and 2). Sodium hydride,[12a] sodium hydroxide, potassium hydroxide, potassium *tert*-butanolate,[7d] and a tetrabutylammonium bromide (NaOH/TBAB)[7e] mixture in refluxing toluene, respectively, gave only moderate yields (45–55%) due to the formation of unidentified by-products under these conditions (Table 1, entries 3–7). We then found that a mixture of KOH and K_3PO_4 gave 4-(3-hydroxy-3-



Scheme 1. General procedure for Sonogashira–Hagihara couplings to obtain 4-aryl-2-methyl-3-butyn-2-ols.



Scheme 2. Deprotection to furnish a terminal acetylene.



Scheme 3. Simple deprotectionleading to terminal acetylenes.

methylbut-1-yn-1-yl)benzoate in quantitative yields after 5 min, when 1 equiv of the starting material, 1 equiv of KOH, and 1 equiv of K_3PO_4 were heated in toluene at reflux temperature (Table 1, entry 8).

We then tested scope and limitations of this method. As shown in Table 2, deprotection by a KOH/K_3PO_4 mixture in toluene can be applied to a broad range of protected arylacetylenes. With one exception (vide infra) all reactions were completed within 5–15 min (TLC control) and required no column chromatography for purification.

As shown, the deprotection is very effective for substrates possessing electron-withdrawing (Table 2, entries 1, 5–8, 11, 12) as well as electron-donating groups attached to the aromatic ring (Table 2, entries 4, 13–15, 17, 18). Methyl esters (entries 1, 5–8), ethyl esters (entries 11, 12, 15), benzyl esters (entry 6), MOM protecting groups (entries 13, 14), carbamates (entry 15), 1,3-dioxane groups (entry 17), and TIPS (entry 16) and tert-butyldiphenylsilyl (TBDPS) protecting groups (entry 18) remain intact under these conditions and give terminal acetylenes in good to quantitative yields.

It is worth mentioning that for 4-aryl-2-methyl-3-butyn-2-ols containing more than one butynol moiety (entries 9 and 12), deprotection of both groups was accomplished within 5–10 min and in good yield. We also compared the method described here with known procedures. As presented in Table 2, the KOH/K_3PO_4 mixture gives better yields in all cases tested. With one exception (vide infra), the reaction timeswere shortened from 1 h,[13c] 2 h,[13a] 4 h, and[12d] 5 h[13d] to 5–15 min. All products were isolated after filtration and evaporation of the solvent in vacuo without application of column chromatography as reported.[1a,8,12,13]

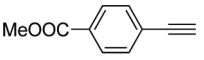
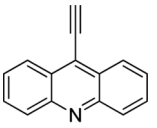
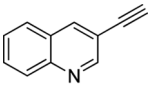
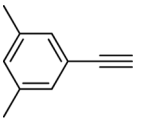
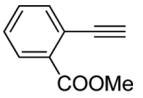
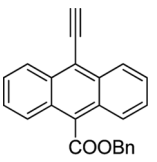
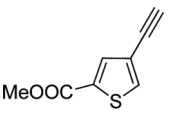
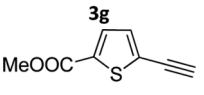
Only for the case of methyl 4-(3-hydroxy-3-methylbut-1-yn-1-yl)thiophene-2-carboxylate did the reaction require 120 min (TLC control) to give methyl 4-ethynylthiophene-2-carboxylate in 78% yield (entry 7). As a comparison, we

Table 1. Deprotection of methyl 4-(3-hydroxy-3-methylbut-1-yn-1-yl) benzoate in the presence of different bases

Entry	Base	Time (h)	Yield (%)[a]
1	K_3PO_4	12	0
2	K_2CO_3	12	0
3	NaH	1	55
4	NaOH	2	45
5	KOH	4	49
6	KOtBu	3	45
7	NaOH/TBAB	12	50
8	KOH/K_3PO_4	<0.1	>99

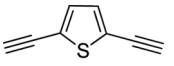
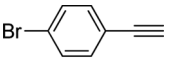
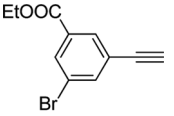
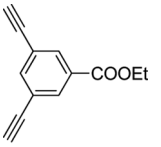
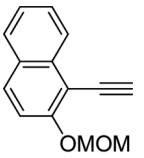
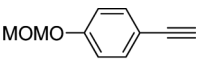
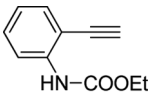
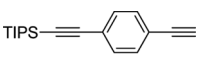
[a]Yields refer to isolated products characterized by spectroscopic data (^1H and ^{13}C NMR, MS, and IR analyses).

Table 2. Preparation of terminal acetylenes by removal of the 2-hydroxypropyl group

Entry	Product	Yield (%)
1	 **3a**	100 (69)[12a]
2	 **3b**	93
3	 **3c**	96 (87)[12d]
4	 **3d**	100 (95)[13a]
5	 **3e**	80 (65)[13b]
6	 **3f**	91
7	 **3g**	78
8	 **3h**	81

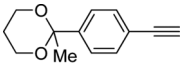
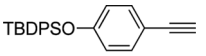
(*Continued*)

Table 2. Continued

Entry	Product	Yield (%)
9	 **3i**	100
10	 **3j**	84 (75)[13c]
11	 **3k**	70
12	 **3l**	76
13	 **3m**	87
14	 **3n**	96
15	 **3o**	89
16	 **3p**	93 (80)[13d]

(*Continued*)

Table 2. Continued

Entry	Product	Yield (%)
17	 **3q**	86
18	 **3r**	100

performed the deprotection with KOH without K_3PO_4 in toluene at reflux temperature, which resulted in the formation of the target compound in only 26% yield.

In summary, we present an efficient and fast method for the synthesis of terminal acetylenes by the deprotection of 4-aryl-2-methyl-3-butyn-2-ols. This method shows good tolerance to a wide range of other functional and protecting groups present in the substrate.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (400-MHz) and Avance III (600-MHz) spectrometers and were taken in dimethylsulfoxide (DMSO-d_6) or $CDCl_3$ at 400 MHz and 600 MHz, respectively. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane ($\delta = 0.00$ ppm). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, and br = broad. Peak assignments were accomplished by results of heteronuclear multiple bond correlation (HMBC), HSQC NMR, and nuclear Overhauser effect spectroscopy (HH-NOESY) measurements. Fourier transform–infrared (FT-IR) spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5% pellets in KBr). The gas chromatography–mass spectrometry (GC-MS) spectra (EI) were recorded either on a Varian 320 GC-MS or on a Varian GC3900 with SAT2100 T mass spectrometer. The electrospray ionization (ESI) mass spectra were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0-V fragmentor voltage unless otherwise noted. The high-resolution (HR)-MS were measured on a Bruker Daltonik Tesla-FT-ion cyclotron resonance mass spectrometer with ESI. Yields are not optimized.

General Procedure for Sonogashira–Hagihara Coupling

The reactions were carried under nitrogen atmosphere. The aryl/heteroaryl bromide, $Pd_2(PPh_3)_2Cl_2$ (1 mol%), and CuI (1 mol%) were suspended in dry Et_3N (20 mL) with stirring. Then 2-methyl-3-butyn-2-ol (1.1 eq.) was added dropwise at ambient temperature. The resulting solutions were then stirred at reflux temperature until complete conversion, as monitored by TLC. Then the mixtures were allowed to cool to room temperature, treated with dichloromethane (50 mL), and filtered

through celite. The organic phases were then dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo. The resulting residues were finally purified by column chromatography (EtOAc–petroleum ether) to afford the products.

Methyl 4-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzoate (2a)

A sample of 30 mmol (6.45 g) of methyl 4-bromobenzoate **1a** gave 29.2 mmol (6.36 g, 97%) of **2a** as light yellow solid: mp 84–85 °C (lit.[12a] 83.5–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (ddd, $J = 1.5$, $J = 2.0$, $J = 8.2$ Hz, 2H; 2-H), 7.46 (ddd, $J = 1.5$, $J = 2.1$, $J = 8.2$ Hz, 2H; 3-H), 3.91 (s, 3H; Me), 2.29 (s, 1H; CH), 1.63 (s, 6H; Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.6$, 131.6, 129.5, 129.4, 127.5, 96.8, 81.4, 65.6, 52.3, 31.4 ppm. IR (ATR, cm^{-1}) 3432, 2993, 2983, 2950, 1711, 1602, 1434, 1404, 1273, 1174, 1166, 1106, 1097, 959, 906, 857, 836; MS (GC-MS) [$C_{13}H_{14}O_3$] 218.2 (calc. 218.1); HRMS (ESI) [$C_{13}H_{14}O_3$] 219.1018 (calc. 219.1021).

General Procedure for the Deprotection Reaction

The reactions were carried under a nitrogen atmosphere. A flask was charged with the protected acetylenes (1 mmol), KOH (1 mmol), K_3PO_4 (1 mmol), and anhydrous toluene (40 mL). Then the flask was immersed into a preheated oil bath. The suspensions were stirred vigorously at reflux temperature until complete conversion, as monitored by TLC. The mixtures were then allowed to cool to rt and filtered through a plug of celite, which was washed several times with toluene. After evaporation of the organic phase to dryness the desired products were obtained.

Methyl 4-Ethynylbenzoate (3a)

A sample of 1 mmol (218 mg) of methyl 4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzoate (**2a**) gave 1 mmol (159 mg, 100%) of the yellowish product **3a**: mp 93–94 °C (lit. [12a] 91–93 °C). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (ddd, $J = 1.5/1.8/8.5$ Hz, 2H; 3-H), 7.55 (ddd, $J = 1.5/1.8/8.2$ Hz, 2H; 2-H), 3.92 (s, 3H; Me), 3.23 (s, 1H; ≡CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.5$, 132.1, 130.1, 129.5, 126.8, 82.8, 80.1, 52.3 ppm. IR (ATR, cm^{-1}) 3242, 1701, 1434, 1310, 1277, 1192, 1174, 1108, 1017, 958, 859, 771, 719, 677, 528, 460. MS (GS-MS) [$C_{10}H_8O_2$] 160.0 (calc. 160.0); HRMS (ESI) [$C_{10}H_8O_2 + Na^+$] 183.0429 (calc. 183.0422).

SUPPORTING INFORMATION

Full experimental details can be found via the "Supplementary Content" section of this article's webpage.

REFERENCES

1. (a) Rosovsky, A.; Forsch, R. A.; Sibley, C. H.; Inderlied, C. B.; Queener, S. F. *J. Med. Chem.* **2004**, *47*, 1475–1486; (b) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 1034–1057.

2. Grimsdale, A. C.; Chan, K. L.; Martin, L. E.; Jokisz, P. G.; Holmes, A. B. *Chem. Rev.* **2009**, *109*, 897–1091.
3. Cheng, Y.-J.; Yang, S.-H.; Hsu, C.-S. *Chem. Rev.* **2009**, *109*, 5868–5923.
4. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; (b) Cecchi, L.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852–4860.
5. (a) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630; (b) Dirk, S. M.; Tour, J. M. *Tetrahedron* **2003**, *59*, 287–294; (c) Merkul, E.; Urselmann, D.; Müller, T. J. J. *Eur. J. Org. Chem.* **2011**, 238–242.
6. (a) Godinez, C. E.; Zepeda, G.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 4701–4707; (b) Lin, B.-N.; Huang, S.-H.; Wu, W.-Y.; Tsai, F.-Y.; Mou, C.-Y. *Molecules* **2010**, *15*, 9157–9173; (c) Unterlass, M. M.; Espinosa, E.; D'Agosto, F.; Boisson, C.; Boisson, F.; Ariga, K.; Khalakhan, I.; Charvet, R.; Hill, J. P. *Chem. Commun.* **2011**, *47*, 7057–7059; (d) Shirakawa, E.; Kitabata, T.; Otsuka, H.; Tsuchimoto, T. *Tetrahedron* **2005**, *41*, 9878–9885.
7. (a) Görl, C.; Alt, H. G. *J. Organomet. Chem.* **2007**, *692*, 4580–4592; (b) Koenig, B.; Pitsch, W.; Klein, M.; Vasold, R.; Prall, M.; Schreiner, P. R. *J. Org. Chem.* **2001**, *66*, 1742–1746; (c) Yelamaggad, C. V.; Hiremath, U. S.; Rao, D. S.; Shankar, P. S. K. *Chem. Commun.* **2000**, 57–58; (d) Kondo, K.; Fujitani, T.; Ohnishi, N. *J. Mat. Chem.* **1997**, *3*, 429–433; (e) Lee, M.; Kim, J.-W.; Peleshanko, S.; Larson, K.; Yoo, Y.-S.; Vaknin, D.; Markutsya, S.; Tsukruk, V. V. *J. Am. Chem. Soc.* **2002**, *31*, 9121–9128.
8. (a) Cross, T. A.; Davis, M. *Synth. Commun.* **2008**, *38*, 499–516; (b) Harada, S.; Takita, R.; Oshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, *43*, 948–950.
9. (a) Rahimi, A.; Pápai, I.; Madarász, Á.; Gjikaj, M.; Namyslo, J. C.; Schmidt, A. *Eur. J. Org. Chem.* **2012**, 754–763; (b) Rahimi, A.; Namyslo, J. C.; Drafz, M. H. H.; Halm, J.; Hübner, E.; Nieger, M.; Rautzenberg, N.; Schmidt, A. *J. Org. Chem.* **2011**, *76*, 7316–7325; (c) Schmidt, A.; Rahimi, A. *Chem. Commun.* **2010**, *46*, 2995–2997.
10. (a) Schmidt, A.; Münster, N.; Dreger, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2790–2793; (b) Schmidt, A.; Beutler, A.; Albrecht, M.; Ramírez, F. J. *Org. Biomol. Chem.* **2008**, *6*, 287–295; (c) Schmidt, A.; Snovydovych, B.; Gjikaj, M. *Synthesis* **2008**, 2798–2804; (d) Schmidt, A.; Beutler, A.; Habeck, T.; Mordhorst, T.; Snovydovych, B. *Synthesis* **2006**, 1882–1894; (e) Schmidt, A.; Mordhorst, T.; Nieger, M. *Org. Biomol. Chem.* **2005**, *3*, 3788–3793; (f) Schmidt, A.; Nieger, M. *Heterocycles* **1999**, *51*, 2119–2126.
11. (a) Albrecht, M.; Nieger, M.; Schmidt, A. Z. *Naturforsch. B* **2012**, *67b*, 103–106; (b) Albrecht, M.; Nieger, M.; Schmidt, A. Z. *Naturforsch. B* **2011**, *66b*, 209–212.
12. (a) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *10*, 1763–1765; (b) Gallagher, W. P.; Maleczka, R. E. *J. Org. Chem.* **2003**, *17*, 6775–6779; (c) Tojo, K.; Arisawa, T.; Aoki, Y.; Terunuma, D. *Bull. Chem. Soc. Jpn.* **2009**, *4*, 519–527; (d) Rodríguez, J. G., de los Rios, C.; Lafuente, A. *Tetrahedron* **2005**, *61*, 9042–9051.
13. (a) Farr, R. N.; Alabaster, R. J.; Chung, J. Y. L.; Craig, B.; Edwards, J. S.; Gibson, A. W.; Ho, G.-J.; Humphrey, G. R.; Johnson, S. A.; Grabowski, E. J. J. *Tetrahedron: Asymmetry* **2003**, *22*, 3503–3516; (b) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *18*, 4940–4948; (c) Pourjavadi, A.; Marandi, G. B. J. *Chem. Res., Synop.* **2002**, *11*, 552–555; (d) Nakano, Y.; Ishizuka, K.; Muraoka, K.; Ohtani, H.; Takayama, Y.; Sato, F. *Org. Lett.* **2004**, *14*, 2373–2376.