Article

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Studies on the Deprotection of Triisopropylsilylarylacetylene Derivatives

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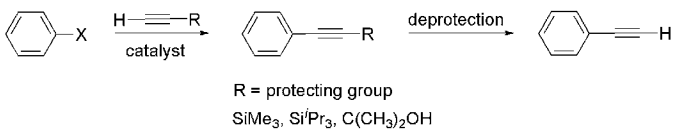
Abstract. Several conditions to deprotect triisopropylsilylarylacetylenes were examined. The triisopropylsilyl protecting group was efficiently removed under mild conditions with 1.5 equiv. of AgF in methanol, a protocol recently reported by Kim. A mixture of $AgNO_3$/KF gave lower yields. Other conditions using combinations of a transition metal, Cu(I), Co(II), Hg(II), and KF failed to react or produced decomposition. The AgF deprotection of TIPS-acetylenes allowed preparation of aryl and heteroaryl terminal alkynes.
Keywords: Desylylation, silver fluoride, alkyne protecting group, TIPS-acetylene.

Resumen. Se evaluaron diferentes métodos para remover el grupo protector en triisopropilarilacetilenos. Se logró remover el grupo protector bajo condiciones suaves usando el método de Kim: tratamiento del alquino protegido con 1.5 equiv. AgF en metanol. La mezcla $AgNO_3$/KF funcionó dando menor rendimiento. Se estudiaron otras condiciones de desprotección en que se combinó un metal de transición Cu(I), Co(II), Hg(II) con KF pero ninguna de ellas funcionó. El tratamiento de un TIPS-alquino con AgF permitió preparar alquinos aromáticos y heteroaromáticos terminales.
Palabras clave: Desililación, fluoruro de plata, grupo protector de alquino, TIPS-acetileno.

Introduction

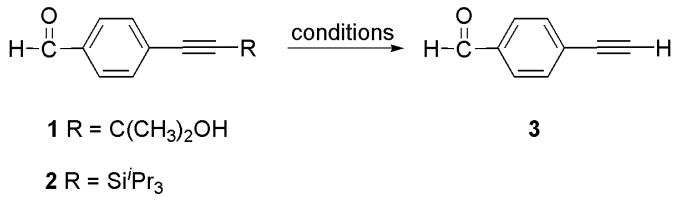
During the course of our work aimed at the synthesis of arylindoles, we needed to prepare a series of arylacetylenes carrying functional groups. Arylalkynes are very useful synthetic intermediates for example in the preparation of indoles [1] and rigid-rod molecules [2] used in electronic and photonic materials [3]. The Sonogashira reaction [4-8] and its variants [9,10] are the traditional methods of choice for preparation of arylalkynes starting from aryl halides [11,12] and a monoprotected acetylene followed by removal of the protecting group (Scheme 1). The protecting group is necessary to make an acetylene surrogate that is easier to handle than gaseous acetylene itself; furthermore, the protecting group blocks one reactive site to accomplish mono substitution in one of the two carbons atoms of the ethynyl moiety. However, the protecting group adds chemical steps for its installation and removal and its use is not atom economic [13,14]. During our work we prepared trimethylsilyl (TMS)-protected arylalkynes bearing functional groups that we intended to further transform. In several instances the TMS group was labile to reaction conditions. [15-17] Thus, it was needed to use other acetylene surrogates more robust than TMS such as triisopropylsilyl (TIPS)-acetylene and the cheap 2-methyl-3-butyn-2-ol reagent as cross coupling partners to obtain arylacetylenes. The utility of these methods depends on one hand on the efficient removal of the protecting group and, on the other hand, on the orthogonal reactivity with functional groups on the arylacetylenes. Thus we tried in our hands reported protection protocols in order to find the best fit for our needs.



Scheme 1.

Since the bulkier TIPS group [15-17] is much less prone to desilylation than the TMS group it seemed an appropiate alternative. However, the procedures for deprotection of TIPS-acetylenes are few. One method, reported by Kim, uses 1.5 equiv. of AgF to remove the TIPS group in acetylenes containing another functional group (alkene, ester, ether, alcohol and, in one example, the ketal of an aminoalcohol). Another method reported by Fallis [18] employs $Cu(OAc)_2$ and Bu_4NF (TBAF). This method seemed less practical since it requires a careful and slow addtion of TBAF by syringe pump. Another seemingly attractive alternative was to use the cheap 2-methyl-3-butyn-2-ol reagent [19, 20] as a cross coupling partner. In this case the removal of the protecting group is carried out by thermal base catalyzed fragmentation.

With these precedents we chose the protected arylalkynes **1** and **2** carrying a reactive aldehyde group as model compounds to test deprotection conditions (Scheme 2). The aldehyde group demands orthogonal reactivity with the acetylene protecting group and the conditions to remove it. Since the commonly employed aldehyde detecting tests of Tollens (Ag(I)) and Fehling (Cu(II)) imply oxidation of the aldehyde group it was not clear at the begining of this work if the Kim´s AgF method was compatible with model compounds **1** and **2**. We present here the results of our studies on removal of TIPS and carbinol acetylene protecting groups forming part of arylacetylene derivatives.



Scheme 2.

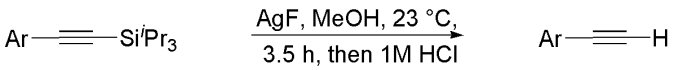
Results and discussion

Initially, the acetylenic alcohol **1** was submitted to the reported thermal base catalyzed fragmentation deprotection protocol [19, 21, 22]. This reaction gave extensive decomposition of the aldehyde starting material and low yield of the desired compound **3** (Table 1, entry a). This result augured a lack of compatibility with many base-sensitive functional groups and the method was not attractive for further exploration. On another attempt, the treatment of **2** with Bu_4NF (TBAF) in refluxing THF [21] (entry b) gave only a low yield of the desired free alkyne **3** with concomitant decomposition of the aldehyde starting material. Similarly, treatment of **2** with HF (entry c) did not give any reaction. These results are likely due to the lower reactivity of the more sterically encumbered TIPS group, as compared to TMS.

At this point we tested Kim´s silver fluoride method [23] and some variants using transition metals that could coordinate with the alkyne group, weakening the C-Si bond. Thus, treatment of **2** with a mixture of KF and $AgNO_3$ at room temperature (entry d) resulted more effective and afforded 52% yield of deprotected **3**. The use of AgF in acetonitrile or methanol [23] (entry e) was even more effective and cleanly afforded the desired terminal alkyne **3** in 81% yield. However, other combinations of transition metals Cu(I), Co(II), Hg(II) with KF (entries f, g, i) did not work. In our studies, even the use of silver dithiocarbamate-KF (entry h) was sluggish, showing that the right combination of the transition metal compound and the fluoride source is vital for the success of the deprotection. Additionally, in our experiment the use of methanol as solvent makes the deprotection reaction faster than acetonitrile. We found for example, that reaction of **2** with AgF in methanol (Table 1 entry e), takes 3.5 h to reach completion *vs.* more than 7 h in acetonitrile or 1:1 methanol-acetonitrile mixtures. The original report stablishes that the reactions runs equally well in both solvents. It is noteworthy that the aldehyde group did not oxidize under the deprotection conditions.

With optimized conditions to remove the TIPS protecting group we carried out the preparation of several terminal arylalkynes (Scheme 3). Thus, deprotection of a series of TIPS-arylacetylenes **4a-c** bearing electron withdrawing groups resulted as expected and afforded arylalkynes **5a-c** in good yields (Table 2). It is noteworthy that deprotection of arylalkynes bearing base sensitive aldehyde and ketone groups (i.e. **2** and **4a**) was realized without any complication. Additionally, heteroarylalkynes **6, 8** and **10** were submitted to deprotection and gave the corresponding terminal alkynes **7**, **9** and **11,** respectively. The low yield observed in the case of pyrimidine **11** is likely due to a water solubility problem and low recovery of the product during aqueous work up of the reaction, since the crude acetylenic product is free of byproducts as observed by TLC and ^1H NMR analysis.

The reported protocol for deprotection of TIPS-acetylenes with AgF is the best method available so far. When the use of TMS as an alkyne protecting group is not satisfactory, the TIPS group is a valid alternative and its removal can be efficiently accomplished with stoichiometric AgF. However, the use of expensive silicon protected acetylene reagents and/or stoichiometric AgF restricts these method to small scale preparations. Another method that uses propiolic acid as a protected alkyne capable to undergo decarboxylative coupling allows the synthesis of diarylalkynes in a more efficient and somewhat less



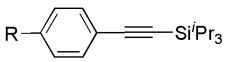
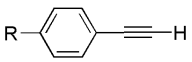
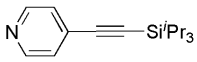
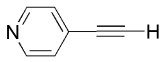
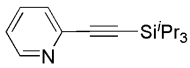
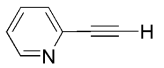
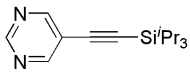
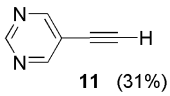
Scheme 3.

Table 1. Optimization of the reaction conditions for deprotection of alkynes **1** and **2**.

Entry	Alkyne	Conditions	Yield of **3**
a	**1**	KOH (4.0 equiv), xylene, 110 °C, 5h	15%
b	**2**	Bu4NF (2.0 equiv), THF, reflux, 0.5 h	25%
c	**2**	10% HF, THF-MeOH, 23 °C	N.R.
d	**2**	KF (1.5 equiv), AgNO3 (1.5 equiv), MeOH, 23 °C, 3.5 h	52%
e	**2**	**AgF 1. equiv, MeOH, 23 °C, 3.5 h. Then 1M HCl**	**81%**
f	**2**	CuI (1.5 equiv), KF (1.5 equiv), MeOH, 23 °C	N.R.
g	**2**	Co(NO3)2 (1.5 equiv), KF (1.5 equiv), MeOH, 23 °C	N.R.
h	**2**	Silver dithiocarbamate (1.5 equiv), KF (1.5 equiv), MeOH, 23 °C	N.D.
i	**2**	HgI2 (1.5 equiv), KF (1.5 equiv), MeCN-MeOH, 23 °C	N.D.

N.R. No reaction was observed. N.D. Yield was not determined; the sluggish reaction proceeded with decomposition of the starting material giving a complex mixture of products.

Table 2. Deprotection of aromatic and heteroaromatic TIPS-acetylenes.

TIPS-acetylene	AgF, MeOH, 23 °C, 3.5 h, then 1M HCl	Product (yield)
		
4a R = $COCH_3$		**5a** R = $COCH_3$ (92%)
4b R = CN		**5b** R = CN (83%)
4c R = NO_2		**5c** R = NO_2 (86%)
		
6		**7** (71%)
		
8		**9** (73%)
		
10		**11** (31%)

expensive way [24]. Thus, a more economical method is still needed.

Experimental Section

Protected arylalkynes **1, 2, 4a-c, 6, 8** and **10** used in this study were prepared according to a general protocol [19, 20]. Reactions were monitored by TLC on Merck silica gel F_{254} plates and spots were visualized with a UV lamp at 254 nm or developed with $KMnO_4$. Column chromatography was performed using Whatman silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded with a Varian VNMR System 400 MHz spectrometer. For ^1H-NMR, tetramethylsilane (TMS δ = 0.0 ppm) in $CDCl_3$ served as an internal standard. For ^{13}C-NMR, $CDCl_3$ (δ = 77.16 ppm) residual peaks served as an internal standard. Infrared spectra were measured on a Perkin-Elmer FT-IR Spectrum GX spectrophotometer.

4-(4-Formylphenyl)-2-methyl-3-butyn-2-ol (1): Amber oil, (yield 96%); IR (film): ν_{max} 3387, 2834, 2736, 2228, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.00 (1H, s), 7.82 (2H, d, J = 8.0 Hz), 7.56 (2H d, J = 8.0 Hz), 1.64 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 135.6, 132.3, 129.6, 129.2, 97.9, 81.4, 65.8, 31.4.

4-(Triisopropylsilylethynyl)benzaldehyde (2): Pale yellow oil, (95% yield); IR (film): ν_{max} 2943, 2728, 2156, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.00 (1H, s), 7.82 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz), 1.13-1.15 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 135.6, 132.7, 129.8, 129.6, 106.0, 95.9, 18.8, 11.4.

General procedure for desilylation of 1-(triisopropylsilyl) acetylenes.

To a degassed solution of 1-(triisopropyl)acetylene (1.0 equiv, 0.1 M in MeOH) AgF (1.5 equiv) was added in the dark, covering the reaction flask with aluminum foil. The reaction mixture was stirred at room temperature (23 °C). After consumption of the starting TIPS-protected acetylene as indicated by TLC analysis, 1 M HCl (3 equiv) was added. The mixture was stirred for 10 min and then filtered. The filtrate was extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane-EtOAc) to afford the terminal alkyne.

4-Ethynylbenzaldehyde (3) [26]: Off white solid, mp 90-91ºC (81% yield); IR (KBr): ν_{max} 3219, 2838, 2740, 2101, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (1H, s), 7.85 (2H, d, J = 8.8 Hz), 7.64 (2H, d, J = 8.4 Hz), 3.30 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 136.0, 132.8, 129.6, 128.4, 82.7, 81.2.

4-Ethynylacetophenone (5a) [25]: Pale yellow solid, mp 67-69 ºC (92% yield); IR (KBr): ν_{max} 3217, 2101, 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 8.8 Hz), 7.58 (2H, d, J = 8.8 Hz), 3.26 (1H, s), 2.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 136.8, 132.4, 128.3, 127.0, 82.9, 80.5, 26.8.

4-Ethynylbenzonitrile (5b) [26]: Off white solid, mp 154-155 ºC (83% yield); IR (KBr): ν_{max} 3238, 2229, 2103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.8 Hz), 3.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.8, 132.1, 127.1, 118.4, 112.4, 82.0, 81.7.

4-Ethynylnitrobenzene (5c) [25]: Pale yellow solid, mp 149-150ºC (86% yield); IR (KBr): ν_{max} 3251, 2105, 1512, 1343, 854, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (2H, d, J = 9.2 Hz), 7.64 (2H, d, J = 8.8 Hz), 3.37 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1, 129.0, 123.7, 82.5, 81.7.

4-Ethynylpyridine (7) [27]**:** Off white solid, mp 95-96 ºC (71% yield); IR (KBr): ν_{max} 3131, 2099, 1593, 1541, 1405 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (2H, dd, J = 4.4 Hz, J = 1.6 Hz), 7.35 (2H, dd, J = 4.4 Hz, J = 1.6 Hz), 3.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 130.4, 126.2, 82.0, 81.0.

2-Ethynylpyridine (9) [26]**:** Brown liquid, (73% yield); IR (film): ν_{max} 3293, 2110, 1584, 1462, 1429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (1H, dq, J = 4.8 Hz, J = 0.8 Hz), 7.67 (1H, td, J = 7.6 Hz, J = 1.6 Hz), 7.49 (1H, dt, J = 7.6 Hz, J = 0.8 Hz), 7.27 (1H, ddd, J = 7.6 Hz, J = 4.8 Hz, J = 1.2 Hz), 3.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 142.4, 136.3, 127.6, 123.5, 82.8, 77.2.

5-Ethynylpyrimidine (11) [26]**:** Off white solid, mp 74-76 ºC (31% yield); IR (KBr): ν_{max} 3168, 2104, 1546, 1410 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 9.18 (1H, s), 8.83 (2H, s), 3.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 157.4, 118.9, 84.6, 77.0.

Acknowledgements

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