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Photo-Cross-Coupling Reaction of Electron-Rich Aryl Chlorides and Aryl Esters with Alkynes: A Metal-Free Alkynylation**

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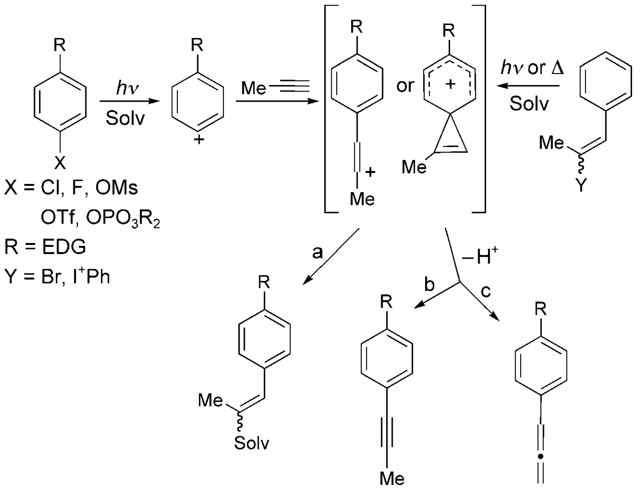
Aryl acetylenes are versatile intermediates in organic synthesis in view of the easy derivatization of their triple bonds[1] and find application in molecular electronics.[2] The elective method for the synthesis of these compounds is the Sonogashira reaction, which involves the Pd/Cu-mediated formation of a C(sp^2)–C(sp) bond. Despite many efforts to improve this method, the most popular protocol in use today still consists of a mixture of an aryl iodide or bromide, a terminal alkyne, $[PdCl_2(PPh_3)_2]$, an amine, and CuI: the same protocol as introduced many years ago by Sonogashira et al.[3,4]

There has been growing interest into extending the reaction to different aryl precursors; for example, aryl triflates (or nonaflates) were introduced about 20 years ago,[5] and more recently aryl tosylates[6] and aryl boronic acids were also used (in the latter case the presence of air is tolerated).[7] However, the inexpensive aryl chlorides have been employed with success in only a few cases, but necessitated the use of high temperatures.[6,8] The use of a single metal compound is possible, and palladium-free[9] and copper-free[10] protocols have also been investigated for some aryl bromides and iodides. In some cases, copper salts cause an adverse effect on the reaction and do not result in the intended catalysis. Thus, copper can either inhibit the reaction[6] or promote oxidative homocoupling.[11] An effective metal-free reaction is clearly desirable and a step in this direction was recently achieved by using microwave-assisted reactions,[12] although satisfying results have been obtained only in one case, namely the reaction between aryl iodides and phenylacetylenes. The Sonogashira reaction generally involves non-activated terminal alkynes, although tetraalkynyl aluminates[13a] and alkynyl trifluoroborates[13b] make the coupling reaction with aryl halides (or triflates) cleaner. A "sila"-Sonogashira reaction starting from alkynylsilanes has also found limited application.[14]

A radically different approach for the synthesis of aryl acetylenes is presented here, and is based on the use of phenyl cations. In the last few years we have demonstrated that these intermediates (in the triplet state) are obtained smoothly by photolysis of aryl halides substitued with electron-donating groups (for example, chlorophenol[15] or fluoroanilines[16]), aryl sulfonates, and aryl phosphates (for example, methoxyphenyl mesylate or *N*,*N*-dimethylaminophenyl phosphate),[17] and add to alkenes to form an aryl–C bond via a phenonium ion.[15a,18] We surmised that phenyl cations would react with triple bonds to yield β-phenylvinyl cations, or more probably cyclic vinylenebenzenium ions (Scheme 1). The last species have been invoked as intermediates in the thermal solvolysis of styryliodonium tetrafluoroborate[19] and in the photoheterolysis of (*E*)-bromostyrene[20] (Scheme 1).



Scheme 1. Hypothesized photogeneration and reaction of the vinylenebenzenium ion. Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl, EDG = electron-donating group.

The usual literature methods for the generation of vinylenebenzenium ions employ a nucleophilic solvent, usually an alcohol. Under these conditions, addition to form an alkoxystyryl derivative occurred (path a, see Scheme 1 for the case of propyne),[19,21] although proton elimination competed to a variable extent and led either to an aryl alkyne (path b) or an aryl allene (path c). Thus, the choice of the conditions is critical so that the desired elimination occurs to form an aryl alkyne.

In view of the above findings, we studied the photolysis of various precursors of the 4-methoxyphenyl cation, namely, the corresponding chloride (**1a**), mesylate (**1b**), triflate (**1c**), diethylphosphate (**1d**), and fluoride (**1e**; 0.05 M) in the presence of 1-hexyne (**2**, a terminal alkyne), ethynyltrimethylsilane (**3**, a partially silylated alkyne), and trimethylsilylpropyne (**4**, a precursor lacking acetylenic hydrogen atoms; 0.5 M). The results of the irradiation experiments are shown in Table 1.

We were happy to find that cross-coupling with 1-hexyne took place upon irradiation ($\lambda_{exc} = 310$ nm, 36 h) of **1** in 2,2,2-trifluoroethanol (TFE) in the presence of an equimolar amount of base (triethylamine, TEA[22]) to yield 4-(1-hexynyl)anisole (**5**) in more than 60 % yield (90 % when using

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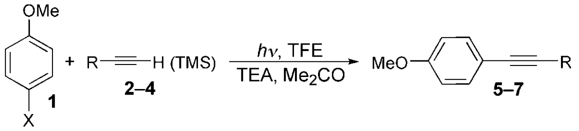
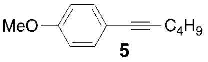
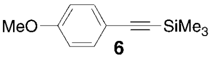
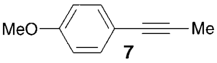
Table 1: Photolysis of 4-methoxyphenyl derivatives **1** (0.05 M) in the presence of 0.5 M alkyne.



1 (X=)	Alkyne	t_{IRR} [h]	ArX consumption [%]	Product	Yield [%][a]
1a (Cl)	$\equiv\!-\mathrm{C_4H_9}$ **2**	36	100	 **5**	62
1b[b] (OMs)		60	75[c]	**5**	73
1c[b] (OTf)		60	80[c]	**5**	83
1d (OPO_3Et_2)		60	80[c]	**5**	90
1e (F)		60	65[c]	**5**	60
1a	$\equiv\!-\mathrm{SiMe_3}$ **3**	36	100	 **6**	71
1b[b]		60	75[c]	**6**	54
1c[b]		60	80[c]	**6**	62
1d		60	80[c]	**6**	70
1a	$\mathrm{Me}-\!\equiv\!-\mathrm{SiMe_3}$ **4**	36	100	 **7**	51 (20)
1b[b]		60	75[c]	**7**	75 (14)
1c[b]		60	80[c]	**7**	67
1d		60	80	**7**	50 (10)

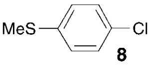
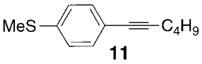
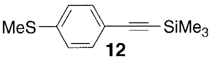
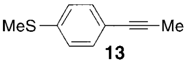
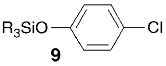
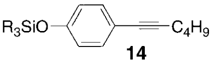
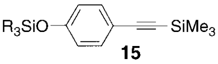
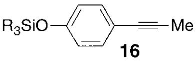
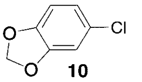
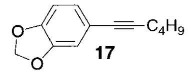
[a] Yields of isolated compounds based on consumed aryl halide or ester. The yield of anisole is shown in parentheses, and is not quoted when less than 5%. [b] Reaction sensitized by 0.9 M acetone and buffered by 0.1 M TEA. [c] The consumption of ArX was not increased after prolonged irradiation.

phosphate **1d**). The use of other solvents, such as MeCN or MeCN/H_2O, gave poor yields.

Esters **1b** and **1c** absorbed poorly at 310 nm and underwent a sluggish reaction under these conditions. Acetone (0.9 M) sensitization was adopted and enabled a high conversion to be obtained (>75% in 60 h), provided that the amount of base was doubled (0.1 M). To our knowledge, these are the first examples reported of an alkynylation reaction using an aryl phosphate,[23] a mesylate, or, noteworthy, an aryl fluoride, which is usually an unreactive derivative.

The photoinduced arylation of alkyne **3** by compounds **1** led to the silicon-containing alkyne (*p*-methoxyphenylethynyl)trimethylsilane, **6**).[24] However, arylation of alkyne **4** occurred with elimination of the trimethylsilyl (TMS) group and gave 4-(1-propynyl)anisole (**7**) in a medium to good yield. When this alkyne was used, the aryl derivatives **1** were in part reduced to anisole, except for the case of triflate **1d**.

Table 2: Photoinduced synthesis of electron-rich aromatic alkynes.

Electron-rich precursor	Alkyne	t_{IRR} [h]	ArX consumption [%]	Product	Yield [%][a]
 **8**	**2**	72[b]	90	 **11**	55
8	**3**	72[b]	80	 **12**	58
8	**4**	72[b]SUP>	100	 **13**	44
 **9**	**2**	45	100	 **14**	51
9	**3**	45	100	 **15**	64
9	**4**	45	100	 **16**	71
 **10**	**2**	30	100	 **17**	52

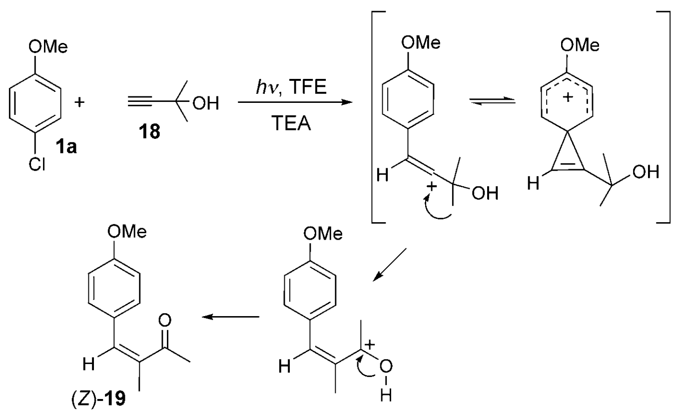
[a] Yields of isolated compounds based on consumed aryl chloride; the corresponding dehalogenated aromatic compounds (<10%) were identified in the irradiated solutions by GC analysis. [b] Irradiation carried out at 254 nm. Cloudy solutions were obtained after irradiation.

Aromatic alkynes could not be used conveniently in this procedure because they absorbed a significant fraction of the incident light and underwent photoreactions to give strongly absorbing products. Thus, irradiation of phenylacetylene in TFE led to darkening and clouding of the reaction mixture; under these conditions the consumption of **1a** after 36 h was limited to 37% and the only significant product was anisole (12%).

The generation of phenyl cations from aromatic compounds substituted with other electron-donating groups[25] was then explored by using the readily accessible chlorides **8–10** (Table 2). The reaction was successful also in these cases (44–71% yield). However, the use of 4-chlorothioanisole **8** resulted in clouding of the solution during the irradiation, which hindered the complete consumption of the halide and prolonged the required irradiation time. This problem was in part overcome by irradiating at 254 nm. Although 4-chlorophenol gave poor results in the reaction, the *tert*-butyldimethylsilyl-protected derivative **9** gave aryl alkynes in 51–71% yield. The chlorinated benzodioxole **10** reacted in a similar way with 1-hexyne and gave arylated compound **17** in 52% yield after 30 h of irradiation.

Finally, we explored the reaction of **1a** with the propargylic alcohol 2-methyl-3-butyn-2-ol (**18**). In this case, an unexpected route was followed and the *Z*-enone **19** was obtained as the only product (35% yield, Scheme 2).

The above results show that aryl alkynes are obtained by reaction of aryl cations with terminal acetylenes or their silylated derivatives. The cations are readily obtained by photolysis of electron-rich aryl esters or aryl halides, with the readily available chlorides being a particularly convenient choice. Furthermore, aromatic compounds bearing an SMe,

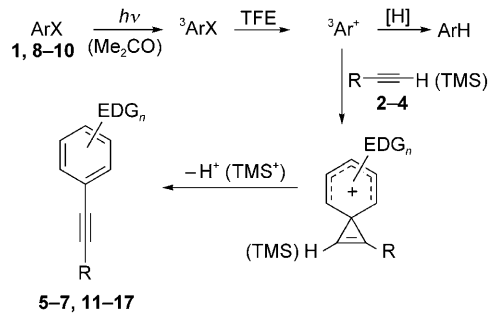


Scheme 2. Addition of the 4-methoxyphenyl cation onto propargylic alcohol **18**.

an *O*-trialkylsilyl (as a protected OH group), or a dioxolanyl group were used for the first time in the generation of aryl cations,[25] thus broadening the scope of the arylation reaction.

Alkynes are known to be less reactive with electrophiles than the corresponding alkenes. However, Mayr et al. reported that 1-hexyne is less reactive by one order of magnitude than 1-hexene in the reaction with (p-$MeC_6H_4)_2CH^+$ at −70 °C,[26a] but that the difference is reduced at higher temperatures. In some cases the reactivity towards the carbenium ion is similar or even higher than that of alkenes.[26b] In the present case, the reactions involving alkynes **1**–**3** required a longer irradiation time (>30 h) than alkenes (14 h),[15a] but this can probably be attributed to a stronger filter effect of the product formed (conjugated phenylalkynes versus alkyl benzenes) rather than to a less-efficient reaction. The photolysis requires a polar (preferably a protic) medium for reaction to occur.[27] TFE was found to be the best solvent for the arylation of alkynes, but the same products were formed in lower yields in MeCN, MeOH, MeCN/TFE, and $MeCN/H_2O$. Among these, $MeCN/H_2O$ (5:1) gave the best results, although reduction of the aryl cations was competitive with the reaction with the alkynes[28] (for example, the reaction between **1a** and **4** gave 34 % of **7** and 30 % of anisole).

The mechanism of the reaction is outlined in Scheme 3. The vinylenebenzenium ion resulting from the trapping of $^3Ar^+$[29,30] by the alkyne does not undergo solvent addition in TFE (a poor nucleophile),[31] nor indeed in a more nucleophilic medium such as $MeCN/H_2O$. Rearrangement to yield allenes also does not compete, and the straightforward formation of the alkynes is by far the preferred pathway and involves elimination of the acetylenic hydrogen atom. Of particular note is that deprotonation is the only process observed in the arylation of ethynyltrimethylsilane—to the exclusion of the elimination of the other potential electrofugal group TMS^+.[32] Nevertheless, when the TMS^+ ion is the only leaving group present (as in the case of **4**), this is eliminated and an aryl alkyne is again formed in a good yield,[33] although in this case reduction of the phenyl cation to anisole plays a greater role.[28]



Scheme 3. Mechanism of the photoinduced metal-free formation of aryl alkynes.

A new cationic path was found in the reaction with propargylic alcohol **18**, where a methyl group migrated onto the vinyl cation intermediate (Scheme 2). In this case the driving force is the stability of the α-hydroxy cation formed, and no deprotonation occurred to give an alkyne. Precedents for the migration of a methyl (or a methylene) group adjacent to a vinyl cation have been reported,[34] but examples that lead to an α-hydroxy cation are rare.[35] Moreover, formation of the enone **19** as the *Z* isomer demonstrates a new route to the synthesis of related compounds which are currently accessible by the Rupe or Meyer–Schuster rearrangement.[36]

To summarize, a metal-free protocol for the mild alkynylation of aromatic compounds substituted with electron-donating groups has been developed. The reaction proceeds via a phenyl cation formed by photoheterolysis and allows for the use of a variety of precursors, such as readily available aryl chlorides as well as aryl esters (mesylates or phosphates). Interestingly, aryl fluorides, which are virtually unreactive under metal catalysis in the Sonogashira reaction, could also be used, although the consumption of the reagent was incomplete. Phenylalkynes are obtained in good, although not excellent, yields in TFE. Despite some limitation, this method has distinct advantages over the thermal alternatives, since the reaction is carried out at room temperature, with no need of a sensitive and/or expensive metallic catalyst or of water-free or oxygen-free conditions, and the experimental procedure is quite simple.[37]

The complete H^+ versus TMS^+ selectivity coupled with the successful application to silylated alkynes when no acetylene proton is present is an appealing characteristic of the reaction. The thermal-catalyzed sila-Sonogashira reaction has been exploited to a limited degree up to now, but the use of a silyl derivative may be advantageous for application to complex derivatives where protection is required, as well as making it easier to handle low-boiling alkynes (for example, **4**).[38] Finally, the synthesis of a β-aryl-substituted enone by addition onto a propargylic alcohol opens up yet a new synthetic pathway.

Experimental Section

Typical procedure for the photochemical synthesis of arylalkynes: A solution of an aryl ester or halide (**1, 8**–**10**, 1.5 mmol, 0.05 M), triethylamine (TEA, 0.05 M), and an alkyne (**2**–**4**, 0.5 M) in TFE (30 mL) was poured into two quartz tubes and purged for 10 min with argon, serum capped, and irradiated with six 15-W phosphor-coated lamps (emission centered at 310 or 254 nm). The photolyzed solution was concentrated under reduced pressure and purified by column chromatography (cyclohexane/ethyl acetate as eluant). Acetone (3 mL, 0.9 M) was added to the reaction mixtures involving esters **1b**,**c** and the amount of TEA was increased to 0.1 M.

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[35] A shift of a dialkylaminophenyl group after addition of the arene–ruthenium(II) derivatives onto propargylic alcohols has been reported; see: D. Pilette, S. Moreau, H. Le Bozec, P. H. Dixneuf, J. F. Corrigan, A. J. Carty, *J. Chem. Soc. Chem. Commun.* **1994**, 409–410.

[36] G. Sartori, A. Sartorio, R. Maggi, F. Bigi, *Tetrahedron* **1996**, *52*, 8287–8296.

[37] For example, the reaction between **1a** and **3** was slower (by about 20%) in an air-equilibrated rather than in an argon-equilibrated solution, but the product distribution did not change significantly.

[38] Only a few reports (all of them using aryl iodides) are available concerning the sila-Sonogashira reaction using trimethylsilylpropine; see: M. Krause, X. Ligneau, H. Stark, M. Garbarg, J.-C. Schwartz, W. Schunack, *J. Med. Chem.* **1998**, *41*, 4171–4176; A. K. Dutta, M. C. Davis, X.-S. Fei, P. M. Beardsley, C. D. Cook, M. E. A. Reith, *J. Med. Chem.* **2002**, *45*, 654–662.