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Visible Light Photo-Arbuzov Reaction of Aryl Bromides and Trialkyl Phosphites Yielding Aryl Phosphonates

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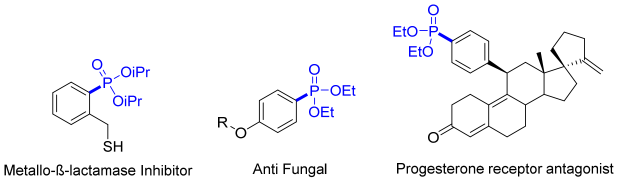
ABSTRACT: Aryl phosphonates are functional groups frequently found in pharmaceutical and crop protection agents. For their synthesis via C-P bond formation typically transition metal catalyzed reactions are used. We report a visible light photo-Arbuzov reaction as an efficient, mild and metal-free alternative. Rhodamine 6G (Rh.6G) is used as photocatalyst generating aryl radicals under blue light. Coupling of the radicals with a wide range of trivalent phosphites gives aryl phosphonates in good to very good isolated yields. The mild reaction conditions allow the introduction of a phosphonate group into complex and sensitive pharmaceutically active molecules, such as benzodiazepams or nicergoline by the activation of a carbon halogen bond.

KEYWORDS: Rhodamine 6G, Phosphonate, Photo-Arbuzov, Visible light, C-P bond formation.

INTRODUCTION

Aryl phosphonates and phosphine oxides are structural motifs found in many pharmaceutically active molecules (Figure 1). In addition, they find applications in organic materials and as synthetic intermediates.[1] The phosphorus containing moiety act as ligand coordinating to transition metals or binding to biological receptors and thereby regulating physiological processes or material functions.[2] The broad use of organophosphorus compounds in different areas of science triggered the development of many methods for their preparation (Scheme 1). Classic synthesis of aryl phosphonates involves transition metal catalyzed cross coupling of $R_2P(O)H$ with a coupling partner via P-H bond activation.[3] Palladium-catalysed C-P coupling has been well established using various precursors such as aryl halides,[4] triflates,[5] boronic acids,[6] aryl sulfonates,[7] and triarylbismuth.[8] Other methods involve nickel and copper catalysed C-P bond formation,[9] but harsh reaction conditions or substrate scope limitations call for the development of new routes for the synthesis of aryl phosphonates. Recently, a combination of transition metal and visible light catalysis was used for the synthesis of aryl phosphonates via C-X bond activation, but expensive metal complexes and iodobenzene or diazonium salts are required as starting materials.[10]



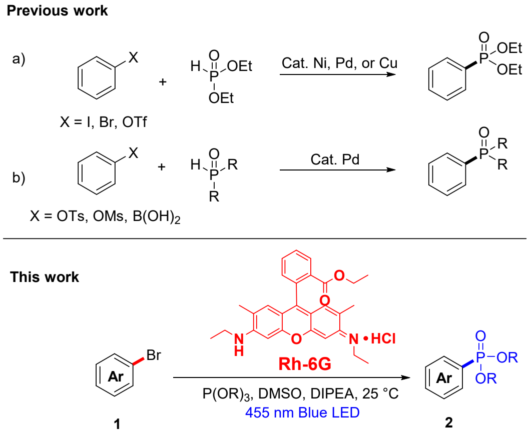
Metallo-ß-lactamase Inhibitor

Anti Fungal

Progesterone receptor antagonist

Figure 1. Aryl Phosphonates in pharmaceutical agents.[1,2]

Visible light photoredox catalysis has emerged into a useful tool for the C-X bond activation by functionalization via photoinduced electron transfer (PET) processes.[11, 12, 13] A highly anticipated application of visible light catalysis is the generation of reactive aryl radicals, which serve as arylating agents to suitable precursors. We have recently introduced the photoredox catalyzed generation of transient aryl radicals from electron deficient arenes, such as diazonium salts[14] or perfluorophenyl bromide[15] by a visible light PET process. Using a consecutive photoinduced electron transfer process (conPET)[16] the scope of starting materials for the generation of aryl radicals was extended to less reactive aryl bromides or aryl chlorides bearing very negative reduction potentials.[17] The xanthene dye rhodamine 6G (Rh.6G)[18] is a particular useful conPET photocatalyst allowing the chromoselective C-X bond activation.[19]



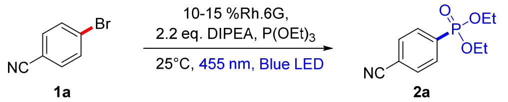
Scheme 1. Rh.6G catalyzed mild C-P bond formation via C-Br bond activation.[3,4,5,6,7,8,9]

Upon irradiation with blue light (455 nm) in the presence of an electron donor under nitrogen atmosphere Rh.6G yields the corresponding excited radical anion (Rh.6G$^{\cdot-*}$),[20,21] which has a reduction potential of ca. -2.4 V vs SCE[19] that is sufficient to activate aryl halides.[16, 22] The initial aryl halide radical anion may cleave into a halide anion and an aryl radical, which can further react with different coupling partners.

RESULTS AND DISCUSSION

As part of our efforts towards the development of mild methods for C-X bond activation, we report here the visible light photoredox catalyzed synthesis of aryl phosphonates via photo-Arbuzov reaction. The photo-Arbuzov reaction is a variation of the classical Michaelis-Arbuzov reaction,[23] and was first demonstrated in 1966 using UV light (quartz mercury vapor lamp) at low temperature and mostly aryl iodides as substrates. The obtained product yields were low to good in the range of 34-90%.[23] To improve the method we aimed to develop a more broadly applicable radical phosphonylation reaction employing visible light photocatalysis using Rh.6G and commercially available bench stable aryl halides.

Table 1. Optimization of the reaction conditions for the photocatalyzed Photo-Arbuzov reaction.

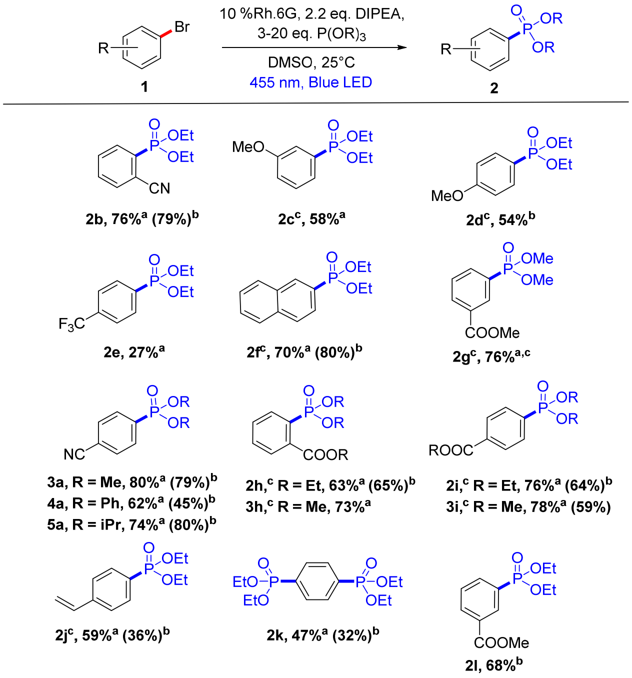


Entry	Solvent	Time (hrs)	$P(OEt)_3$	Yield %[a]
1	DMSO	6	20 eq.	35
2	DMSO	12	20 eq.	52
3	DMSO	17	20 eq.	71
4	DMSO	17	3 eq.	76
5	DMSO	18	5 eq.	76
5	CH_3CN[b]	18	20 eq.	93
6[c]	DMSO	18	20 eq.	34
7[d]	DMSO	18	20 eq.	0
8[e]	DMSO	18	3 eq.	36
9[f]	DMSO	18	3 eq.	Traces
10[g]	DMSO	8	3 eq.	76
11[h]	DMSO	21	3 eq.	52
12[i]	DMSO	18	3 eq.	40
13[j]	DMSO	18	3 eq.	28

[a] Isolated yield. [b] Substrate specific. [c] Reactions performed in the absence of DIPEA. [d] Reactions performed in the absence of light. [e] Without degassing [f] Under O2 atmosphere [g] In PTFE flow reactor. $P(OEt)_3$ = triethyl phosphite. [h] Reaction performed with 2.2 mmol. [i] Reaction with 5% $Ru(bpy)_3Cl_2$ x 6 H_2O as photocatalyst [j] Reaction with 5% $Ir(ppy)_3$ as photocatalyst. DIPEA = *N,N'*-disopropylethylamine. LED = light emitting diode. *10 mol % of photocatalyst was used unless mentioned otherwise. Reactions were monitored using gas chromatography.

We began our investigations towards a visible light mediated photo-Arbuzov reaction with irradiating 4-bromobenzonitrile in DMSO in the presence of Rh.6G and *N,N*-diisopropylethylamine (DIPEA), as sacrificial electron donor, under nitrogen atmosphere to generate a highly reactive *p*-cyano phenyl radical. Trapping of the radical with triethyl phosphite delivered the corresponding diethyl (4-cyanophenyl) phosphonate in 71% (see table 1, entry 3, 4, 5). Reactions were also performed in the presence of air (entry 8), which reduced the product yield significantly, and under oxygen (entry 9), giving only traces of the product. Typical test reactions were run at 0.1 – 0.3 mmol scale, but larger scales are possible. A reaction done at 2.20 mmol scale gave 52% isolated product and in a flow reactor 76 % product yield.

The same reaction conditions with different triethyl phosphite concentrations did not show much influence on the isolated yield. The reaction in CH_3CN gave excellent conversion, but it was limited to the standard substrate. In the absence of DIPEA only traces of the desired product were observed. This might be rationalized by a single electron transfer from the trapping reagent to the excited photocatalyst, but the reaction proceeds very sluggish with minor amounts of product formed.



[a] Yield of product with 20 eq. of the trapping reagent. [b] Yield of the product with 3 eq. of the trapping reagent. [c] 15% of the Rh.6G used. For detailed information on the reaction conditions, see the supporting information.

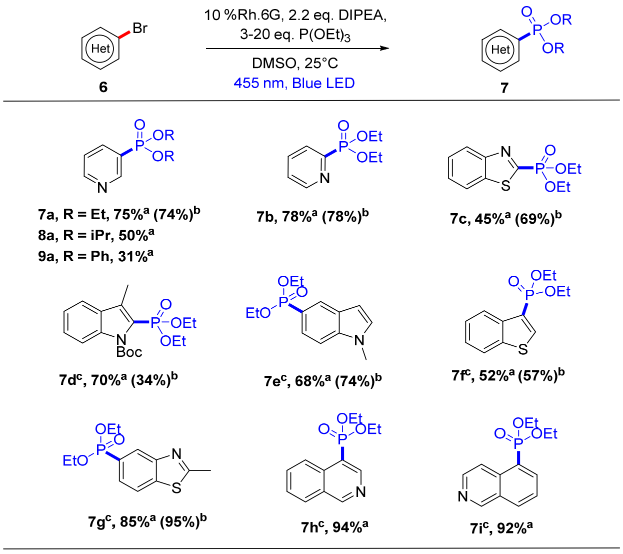
Scheme 2. Scope or aryl bromide for Photo-Arbuzov reaction.

Based on the optimized reaction conditions, we explored the scope of visible light induced phosphonylation of aryl bromides further.

The reaction proceeds smoothly with a wide functional group tolerance. Mostly, 10-15 mol% loading of the catalyst was required for a complete conversion of the substrate. Precursors bearing nitrile, ester, methoxy, vinyl functionality (**1a-1l**) gave the phosphonylated product in good yield. In general, electron deficient arenes (**1a, 1b, 1g, 1h, 1i**) showed higher conversion to the corresponding phosphonylated product than electron-rich arenes (**1c, 1d, 1j**). Contradictory to the observation, 4-bromobenzotrifluoride (**1e**) gave the corresponding phosphonate in a yield of only 27%. One-pot conversion of 1,4 dibromobenzene (**1k**) to the corresponding di-phosphonate was achieved in moderate yield. Also, 4-bromostyrene (**1j**) gave the interesting building block **2j** in good yield. Apparently, bromobenzonitriles (**1a, 1b**) are more reactive substrates in the photocatalytic phosphonylation reaction, with comparatively shorter reaction time (17h) required for a complete conversion.

Different phosphites, such as $P(OMe)_3$, $P(OPh)_3$ and $P(OiPr)_3$, were coupled with aryl bromides under the optimized reaction conditions (Scheme 2, entry **2g**, **3a-5a**, **3h**, **3i**, **2l**). Varying electronic properties and steric bulk were tolerated: aryl-dimethyl, diphenyl and di-isopropyl phosphonates were synthesised in 62 to 80% yield.

Subsequently, we explored the use of heteroaryl bromides in this photo-Arbuzov reaction protocol. To our delight, a range of six membered and fused heterocyclic bromides were suitable for the coupling with triethyl phosphite as well as other trialkyl phosphites (Scheme 3) in moderate to excellent yield. The ability of the catalytic system to activate electron-rich as well as electron-deficient heteroarenes demonstrates a remarkable scope. Bromopyridine analogues **6a** and **6b** showed fast conversion to the corresponding phosphonates (14h) with 75-78% yield.

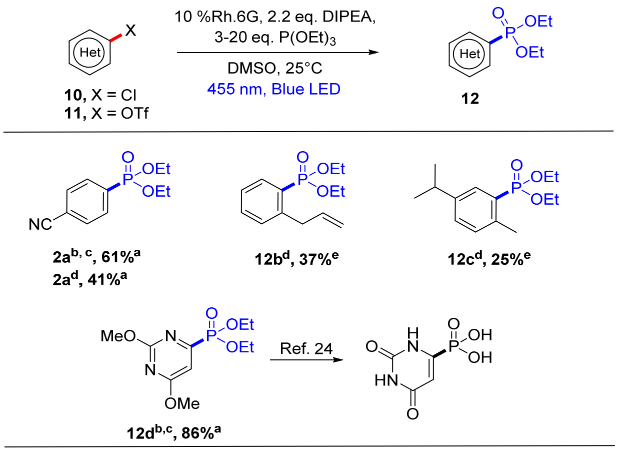


Starting material in all the cases 0.1 – 0.3 mmol, reaction time 15-33 h. [a] Yield of product with 20 eq. of trapping reagent. [b] Yield of the product with 3 eq. of the trapping reagent. [c] 15% of the Rh.6G used. For detailed information on the reaction conditions, see the supporting information.

Scheme 3. Scope of visible light induced phosphonylation of heteroaryl bromides.

In addition, electron rich heterocycles such as **6d**, **6e**, **6f**, and **6g** gave excellent conversion. Moreover, isoquinoline derived substrates such as **6h** and **6i** showed exceptionally good conversion to the corresponding phosphonates **7h** and **7i** giving 94 and 92% yield, respectively, in 33 h. (Scheme 3).

Next, we examined aryl chloride and aryl triflates as aryl radical precursors under the optimized conditions (Scheme 4). A longer reaction time was required for the conversion of *p*-chlorobenzonitrile (**10a**) to the corresponding phosphonate, because of the more negative reduction potential of the substrate.[16,21] The reaction with aryl chlorides and aryl triflates gave the corresponding phosphonate **12a**[c] in 61% and **12a**[d] in 41% yield. A triflate derivative of the natural product Carvacrol (**11c**) was converted to its diethyl phosphonate analogue **12c**[d]. The dimethoxy-protected uracil **10d** gave the expected product **12d** in 86% yield. This compound can be further converted to the phosphoric acid analogue of uracil.[24]

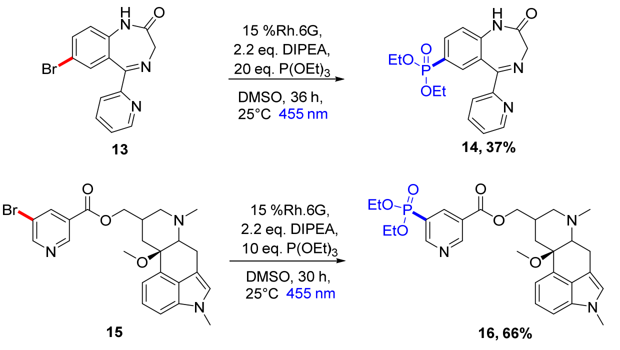


Amount of starting material in all cases 0.1 – 0.3 mmol, reaction time 24-68 h. [a] Yield of product with 20 eq. of trapping reagent. [b] 15% of the Rh.6G used. [c] Aryl chloride as a substrate. [d] Aryl triflate as substrate. [e] Yield of product with 3 eq. of trapping reagent. For detailed information on the reaction conditions, see the supporting information.

Scheme 4. Scope of aryl chloride and aryl triflates for the visible light induced phosphonylation.

Encouraged by the results, we applied the developed conditions to the late stage metal-free phosphonylation of pharmaceutically active molecules (Scheme 5). We chose bromazepam, a benzodiazepine derivative and anti-anxiety agent and nicergoline, an ergot alkaloid used for the treatment of metabolic vascular disorders, both containing a bromide group in the aryl ring.

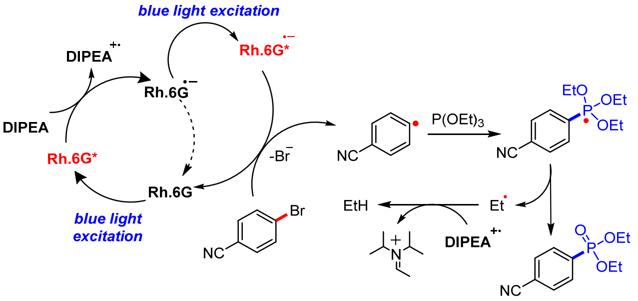
The phosphonylation of bromazepam **13** gave the respective azepam phosphonate (**14**) in 37% isolated yield, tolerating the amide and imine functional groups. Likewise, the reaction of highly functionalized nicergoline **15** yielded the phosphonylated product in 66%.



Scheme 5. Late stage phosphonylation of biologically active compounds.

PROPOSED MECHANISM

A proposed mechanism for the visible light induced Rh.6G catalysed photo-Arbuzov reaction is outlined in Scheme 6.



Scheme 6. Proposed mechanism for the visible light photo-Arbuzov reaction.

Upon blue light photoexcitation Rh.6G photooxidizes DIPEA giving the radical anion Rh.6G$^{\cdot-}$ and the radical cation of DIPEA$^{\cdot+}$. Continuous irradiation of the radical anion Rh.6G$^{\cdot-}$ with blue light triggers a single electron transfer from the excited Rh.6G$^{\cdot-*}$ [17,19,20] to the aryl halide producing the transient Ar-Br$^{\cdot-}$radical anion and regenerating the neutral Rh.6G completing the catalytic cycle. Further, Ar-Br$^{\cdot-}$ undergoes fragmentation to release an aryl radical and a bromide anion; this process is in competition with a non-productive back electron transfer. The aryl radical reacts with trivalent phosphorous forming a C-P bond and the unstable phosphoranyl radical.[25] Release of an ethyl radical and rearrangement results in the formation of the target aryl phosphonate. The reactive ethyl radical may abstract a hydrogen atom from DIPEA$^{\cdot+}$ or the solvent. In competition with the desired C-P bond forming reaction, the aryl radical can abstract a hydrogen atom from DIPEA$^{\cdot+}$ or the solvent giving the respective reduced product. This process is confirmed by the gas chromatography mass spectrometry (GS-MS) data showing the formation of diisopropylamine and the dehalogenated arenes as by-products in the reaction mixture. However, an alternative mechanism forming the aryl phosphonate via oxidation of the radical to a phosphonium intermediate and elimination of ethene cannot be fully excluded at the present stage of the mechanistic investigations.[26]

CONCLUSION

We have demonstrated the metal-free visible light driven phosphonylation of aryl halides to their corresponding phosphonates. The mild reaction conditions are compatible with many functional groups and the scope of trialkyl phosphites and halogenated heteroarenes is broad providing various phosphonates with consistent yields. Furthermore, the method allows a late stage functionalization of biological active aryl halides that can be converted into the phosphoric acid analogues. We believe this new photoredox C-P bond formation via a visible light photo-Arbuzov reaction will find applications in pharmaceutical and academic research.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the http://pubs.acs.org."
General information, experimental procedure, characterization of the compounds, and copies of ^{1}H NMR, ^{13}C, NMR, ^{31}P NMR. Reaction setup

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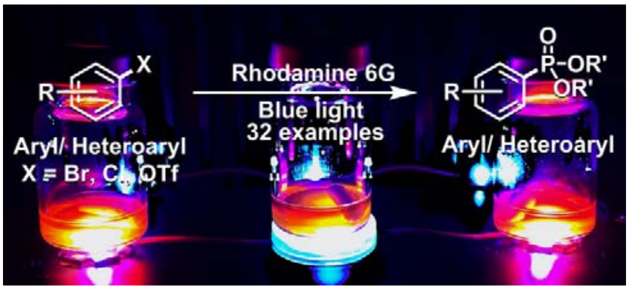
[26] The reaction conversion was monitored by gas chromatography (GC) and GCMS analysis, but the boiling points of ethane (formed in the reaction mixture), ethane and ethyl bromide are too low (38 °C) to be detected by our instruments. Therefore, we cannot fully exclude alternative elimination mechanisms.

TOC graphic


R
X
Aryl/ Heteroaryl
X = Br, Cl, OTf
Rhodamine 6G
Blue light
32 examples
O
P-OR'
OR'
R
Aryl/ Heteroaryl