Expeditious synthesis of bioactive allylphenol constituents of the genus *Piper* through a metal-free photoallylation procedure†

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Nine bioactive allylphenol (anisole) derivatives (*e.g.* eugenol, safrole and asaricin) present in several plants of the genus *Piper* have been synthesized in medium to high yield *via* aryl cation intermediates. This expeditious metal-free procedure involves the irradiation of the corresponding chlorophenols or chloroanisoles in a polar solvent (MeCN or, better, TFE or aqueous acetonitrile) in the presence of allyltrimethylsilane. Estragole has also been synthesized starting from the corresponding fluoroderivative and diazonium salt, though in a lower yield.

Introduction

The genus *Piper*, belonging to the family Piperaceae, has over 700 species, many of which are important for the food and pharmaceutical industries.[1] Indeed, about 600 bioactive compounds have been extracted and characterized from plants of this genus, most of which are allylphenols.[1] These compounds have fungicidal, nematicidal, antimicrobial and molluscicidal activity and are used in the manufacturing of perfumes and fragrances. Furthermore, this class includes genotoxic and carcinogenic compounds, such as safrole, methyleugenol and estragole, which have been recently investigated in order to clarify their interaction with DNA.[2]

The typical approach for the synthesis of these compounds involves aryl–allyl C–C bond formation. Since the direct cationic allylation is generally inefficient or unselective,[3] cross-coupling reactions are preferentially used. Some efficient procedures starting from aryl halides (mostly iodides or bromides) have been reported and make use of either aryl Grignard[4a] or arylzinc[4b] derivatives or involve catalysis by nickel,[4c] cobalt[4d] or palladium,[4e] *e.g. via* the Stille reaction (Scheme 1a). Arylboronic compounds have been likewise used in the Pd mediated reactions with allyl acetate.[4f] Despite the high yield obtained in several cases, these metal-mediated reactions have significant drawbacks. In many cases these occur under strictly anhydrous conditions and/or at a high temperature and involve the use of expensive and sensitive ligands, further additives or a large amount of the catalyst. Furthermore, if the target molecule contains free hydroxyl groups a protection–deprotection sequence must be carefully planned[4c,5a] since a considerable product loss may occur in the deprotection step.[5b] At any rate, when the products are meant for pharmaceutical use the toxic organometallic compounds must be thoroughly removed. Accordingly, an expeditious metal-free synthesis of allylphenols starting from unprotected halophenols (preferably the less expensive chlorophenols) is desirable.
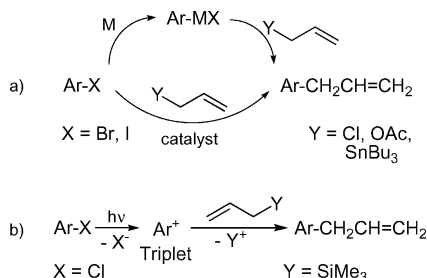
We recently reported that 4-hydroxy- and 4-methoxyphenyl cations are generated by the photolysis of 4-chlorophenol and 4-chloroanisole, respectively.[6a] These are formed in the *triplet* state and readily add to olefins,[6a] while being unreactive toward neutral n donors; a fact that allows the use of alcohols as solvents. We reasoned that the reaction of these cations with allyltrimethylsilane (ATMS) would lead to the corresponding allylated aromatics after elimination of the trimethylsilyl cation, a good electrofugal group (Scheme 1b). We had previously obtained allylated derivatives from the irradiation of related compounds in a few cases.[7] On the other hand, we noticed that the thermal cross-coupling of phenyl halides with ATMS gave both silicon-free allylbenzenes and silylated derivatives, although conditions could be found for making the first process exclusively.[8]

Thus, planning the synthesis of allylated polyphenols and their derivatives, such as those present among the bioactive compounds of plants of the genus *Piper*, offers the opportunity to test the arylation reaction *via* a phenyl cation on a larger choice of precursors.
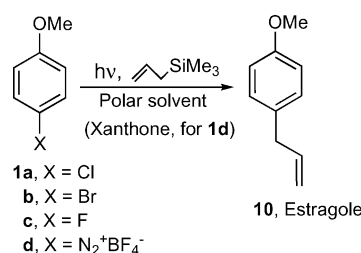
Results and discussion

As mentioned above, the target compounds we considered were polyfunctional phenols or their ethers or acetals. The synthesis involved the photochemical generation of the phenyl cation in the presence of ATMS. We found that irradiation ($\lambda = 310$ nm) of a series of aryl chlorides bearing one to three OH(OR) groups (**1a** and **2–9**, 0.05 M) in the presence of an excess of the allyltrimethylsilane (0.5–1 M) in 2,2,2-trifluoroethanol (TFE) consistently gave allylated benzenes (formulae **10–18**, see Scheme 2 and Scheme 3). The halophenols (anisoles) used as
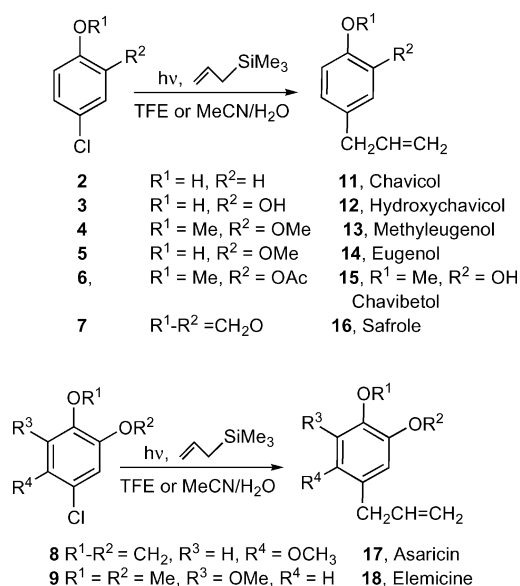
Scheme 1

Scheme 2

R^1, R^2 substituents for Scheme 3 compounds:

2	R^1 = H, R^2= H	**11**, Chavicol
3	R^1 = H, R^2 = OH	**12**, Hydroxychavicol
4	R^1 = Me, R^2 = OMe	**13**, Methyleugenol
5	R^1 = H, R^2 = OMe	**14**, Eugenol
6,	R^1 = Me, R^2 = OAc	**15**, R^1 = Me, R^2 = OH Chavibetol
7	R^1-R^2 =CH$_2$O	**16**, Safrole

8 R^1-R^2 = CH$_2$, R^3 = H, R^4 = OCH$_3$ **17**, Asaricin
9 R^1 = R^2 = Me, R^3 = OMe, R^4 = H   **18**, Elemicine

Scheme 3

starting materials were either of commercial origin or were easily available by controlled chlorination reactions (see Experimental for details). The desired allylated products were isolated by column chromatography in yields ranging from 47% to 87%.

Previous studies had shown that TFE is the elective solvent for cationic arylations due to the excellent ion stabilization power.[6] With some substrates an improved yield was attained when the amount of ATMS was increased to 1 M. However, TFE is rather expensive and its use requires that a base (Cs$_2$CO$_3$, in an equivalent amount with the phenyl halide) is added for a clean reaction to occur. Looking for an alternative, we tested the irradiation of the same substrates in a less expensive polar solvent, such as MeCN. In this medium the yields were found to be highly variable depending on the structure, with a maximum of 60% and a minimum as low as 6%. This was due to the incomplete conversion of the starting material. However, we were delighted to find that allylated derivatives **10–18** were consistently obtained in reasonable yields (40–71%, see Table 1) when using MeCN–water mixed solvents. In this case, these yields were comparable to and in some cases (*e.g.* with estragole) even higher than those observed in TFE, with a dramatic enhancement with respect to neat MeCN. When the aqueous solvent was used, the work up procedure was modified and involved continuous solvent extraction. It is noteworthy

that a clean reaction was obtained in the absence of Cs$_2$CO$_3$; apparently the basicity of water was sufficient for buffering the acidity liberated during the reaction.

The strategy for the synthesis of chavibetol (**15**) was slightly modified since the 2-methoxy-4-chlorophenol precursor was difficult to prepare. However, irradiation of the more easily accessible phenyl acetate **6** in the presence of ATMS caused deprotection of the phenoxy group together with allylation and gave directly the desired product **15** (see Experimental for details).

The scope of the reaction was further tested by exploring the effect of the nucleofugal group in the photo-heterolysis. Thus, the photochemical synthesis of estragole (**10**) was extended to further potential precursors of the phenyl cation,[9] namely *p*-bromoanisole **1b**, *p*-fluoroanisole **1c** and *p*-methoxybenzenediazonium tetrafluoroborate **1d**.[10] *p*-Bromoanisole **1b** was rapidly photodegradated but no allylation products were detected, while reduction to anisole was by far the main pathway (*ca.* 40–50% yield). *p*-Fluoroanisole (**1c**) was photostable when irradiated in MeCN but was completely (in TFE) or partially (in MeCN–H$_2$O) consumed in the other solvents and gave **10**, though in a lower yield and after a long irradiation time (36 h *vs* 14 h with respect to **1a**). As for diazonium salt **1d**, xanthone sensitized irradiation (at 360 nm) in the presence of ATMS led to a decomposition faster than that of the above halides (3 h) and gave **10** in moderate yields.

Finally, preliminary studies of the scale up of this synthetic procedure were carried out. Thus, estragole and chavicole were synthesised in a >3 mmol scale in aqueous MeCN using an immersion-well photoreactor (medium pressure, mercury arc). Under these conditions, the irradiation time was shorter (1.5 to 9 h), the isolated yields obtained were of *ca.* 70% and the concentration of the starting material could be increased up to 0.1M with only a small decrease of the yield (see Table 1). With these amounts of the end products the most practical purification was bulb to bulb distillation.

The successful synthesis of compounds **10–18** confirms that aryl cations are smoothly obtained by irradiation of chlorinated electron-rich aromatics, according to the mechanism outlined in Scheme 4, and are convenient synthetic intermediates. Both chlorides (ArCl, **1a–9**), and fluoride (**1c**, only in protic solvents)[11] undergo heterolytic photofragmentation of the aryl–halide bond *via* the triplet state (^{3}ArCl or ^{3}**1c**). The aryl cation (^{3}Ar$^+$) adds to allyltrimethylsilane, giving a phenonium ion[6a,7] and allylated derivatives **10–18** after trimethylsilyl cation cleavage.

The use of allyltrimethylsilane (ATMS) ensured a straightforward formation of the desired allyl benzenes as the only products

Table 1 Photochemical synthesis of allylphenols and anisoles **10–18**

Precursor	Solvent					
	TFE		MeCN		MeCN–H$_2$O	
	Time/h	Yield^a (%)	Time/h	Yield^a (%)	Time/h	Yield^a (%)
1a	14	**10**, 64	26	**10**, 60	24, 9^{b,c}	**10**, 75, 66^{b,c}
2	14	**11**, 87	26	**11**, 22^d	20, 1.5^b	**11**, 61, 71^b
3	24	**12**, 47^e	26	**12**, 20^f	26	**12**, 43
4	20	**13**, 51	26	**13**, 13^d	26	**13**, 45
5	18	**14**, 73^e	26	**14**, 36	22	**14**, 61
6	18	**15**, 57^e	26	**15**, 6^d	22	**15**, 40
7	14	**16**, 77	26	**16**, 54^d	32	**16**, 55
8	18	**17**, 73	26	**17**, 43	32	**17**, 52
9	24	**18**, 58^f	34	**18**, 40^d	36	**18**, 54
1b	14	^{f,g}	14	^{f,g}	14	^{f,g}
1c	36	**10**, 40	26	^{h}	36	**10**, 28^{d,i}
1d^j	3	**10**, 50	3	**10**, 35	3	**10**, 35

^{a} Isolated yield. ^{b} Reaction carried out in an immersion-well reactor. Products isolated by bulb to bulb distillation. ^{c} **1a**, 0.1 M. ^{d} Partial consumption of the starting material. ^{e} ATMS 1 M. ^{f} Complex mixture of products. ^{g} Anisole was formed in variable amounts at the expense of estragole **10** (see text). ^{h} No photodegradation of **1c** occurred. ^{i} Water 4.5 M as a cosolvent. ^{j} **1c**, 0.01 M; reaction in the presence of xanthone 0.05 M.
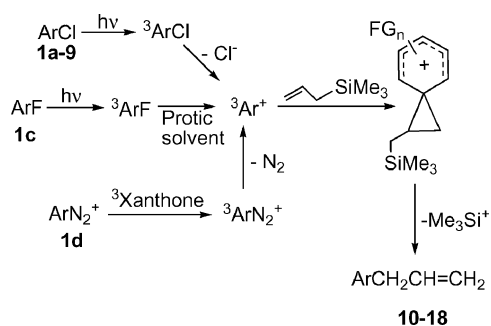
Scheme 4

and avoided competitive reactions from the phenonium ion, such as nucleophilic addition by the solvent or Wagner–Meerwein hydride and alkyl migration observed in other cases.[6,12] This is due to the fact that the trimethylsilyl cation is an excellent electrofugal group. Furthermore, the silyl group enhances the nucleophilicity of the alkene, as recently evidenced by Mayr and coworkers.[13] This is important, because good nucleophiles make the initial cationic arylation possible also in non-protic solvent, possibly *via* an exciplex between the excited state of the aryl halide and the nucleophile.[14] We noticed that allyltributylstannane has been succesfully used in metal mediated allylations, but the high toxicity and the high price of this reagent militate against this choice. On the contrary, ATMS can be conveniently used[15] because of its low toxicity and high volatility.

Cation ³Ar⁺ is obtained also from diazonium salt **1d** after energy transfer from triplet xanthone. The fact that no estragole is formed from bromide **1b** indicates that the C–Br bond undergoes photohomolysis rather than photoheterolysis. The thus formed 4-methoxyphenyl radical abstracts hydrogen from the medium and gives anisole as the main product. Hence, with a weak aryl–X bond, homolytic fragmentation yielding a phenyl radical becomes a viable path, as it has been postulated for the photolysis of bromo and iodophenol in aqueous alkali.[16] and for the irradiation of *p*-bromo- and *p*-iodoanisole in MeOH, where photoreduction was again efficient.[17]

In the synthesis of compound **15** from **6**, the concurrent elimination of an acetyl group reasonably involves radicalic photocleavage of the aryl ester group[18] and this allows skipping the deprotection step that would otherwise be required.

Conclusions

In conclusion, the arylation procedure *via* a photogenerated phenyl cation from Ar–Cl heterolysis has now been applied to aromatic derivatives bearing one to three electron-donating groups (hydroxy, methoxy or dioxolanyl), with allyltrimethyl-silane as the nucleophile for obtaining of a range of alkylated aromatics. The easy preparation of the chloride precursors and the use of MeCN–water as the solvent are further advantages. This expeditious synthesis is experimentally quite simple and can be carried out on a reasonable scale for laboratory preparations, *e.g.* for the synthesis of natural products, such as the present bioactive allylphenols. In general, this photo S$_N$1 reaction is a promising alternative to metal mediated reactions. When applied to allyltrimethylsilane, thermal arylations involve the use of the more expensive aryl iodides or triflates under palladium catalysis and require a higher temperature (50–60 °C) and controlled conditions in order to direct the reaction towards regioselective allylation.[8] Furthermore, activation of the strong aryl–fluoride bond is feasible, as demonstrated in the case of **1c**. Only a few examples of aryl–carbon bond formation starting from **1c** have been previously reported. These involve photocyanations,[19a] substitution reactions by α-cyano carbanions[19b] and the nickel catalyzed Kumada–Corriu cross-coupling with Grignard reagents.[19c] This reasonably effective photochemical activation of aryl fluorides, remarkably applied to electron rich aromatics, is a breakthrough in a field presently limited to electron deficient substituted aromatics.[20]

Experimental

General

NMR spectra were recorded on a 300 MHz spectrometer. The attributions were made on the basis of ¹H and ¹³C NMR, as well as DEPT-135 experiments; chemical shifts are reported in ppm downfield from TMS. The photochemical reactions were performed by using nitrogen-purged solutions in quartz tubes and a multilamp reactor fitted with six 15 W phosphor-coated lamps (maximum of emission 310 nm, 360 nm for **1c**) for the irradiation. Allyltrimethylsilane was freshly distilled before use. Compounds **1a–c**, **2** and **7** were commercially available and used as received. Diazonium salt **1d** was prepared from *p*-methoxyaniline by a known procedure.[21] Phenylchlorides **3–5** were obtained by SO$_2$Cl$_2$ chlorination.[22] Derivative **8** was synthesized from sesamol through a two step reaction[23] and **9** was prepared from 3,4,5-trimethoxyaniline *via* a Sandmeyer chlorination (47% yield). Physical and spectroscopical data of products **10**,[24] **11**,[25] **12**,[26] **13**,[27] **14**,[27] **15**,[28] **16**,[29] **17**[30] and **18**[31] were of a satisfactory fit with those reported in the literature.

2-Acetoxy-4-chloro-1-methoxybenzene (6)[32]. Compound **6** was obtained using the procedure described by Higashiya.[33] NCS (2.1 g, 16.2 mmol) was added to a solution of 2-acetoxyanisole[34] (0.9 g, 5.4 mmol) in dry CH$_3$CN and the resulting mixture was stirred for 14 d at rt. The solvent was then evaporated and the residue thus obtained washed with toluene (3 × 20 ml). The organic layers were washed with aqueous Na$_2$SO$_3$ (2 × 20 ml) and water (20 ml) and then dried over MgSO$_4$, filtered and evaporated. The crude residue was distilled under a vacuum to give 825 mg of a pale yellow oil (76% yield).

6: δ_H(CDCl$_3$) 2.30 (s, 3H), 3.80 (s, 3H), 6.90 (d, 1H, J = 9 Hz), 7.15 (d, 1H, J = 2.5 Hz), 6.90–7.20 (dd, 1H, J = 2.5 and 9 Hz). δ_C(CDCl$_3$, 75 MHz) 20.4 (CH$_3$), 56.0 (CH$_3$), 113.0 (CH), 123.2 (CH), 125.1, 126.5 (CH), 140.0, 149.9, 168.5 (CO). ν_{max}(neat)/cm^{-1} 2979, 1669, 1388, 1256, 1094; anal. calc. for C$_9$H$_9$ClO$_3$: C, 53.88; H, 4.52. Found: C, 54.0; H, 4.4%.

Photochemical allylation of aryl halides: general procedure. A solution of compounds **1** to **9** (1.5 mmol), allyltrimethylsilane (15 mmol, except when indicated) in 30 ml of the chosen solvent was irradiated at 310 nm (in TFE, 0.75 mmol Cs$_2$CO$_3$ were added). The resulting solution was purified by column chromatography (cyclohexane–ethyl acetate). In the case of a 5 : 1 mixture of MeCN–water as the solvent, the photolized solution was extracted with CH$_2$Cl$_2$ in a liquid–liquid extractor before evaporation and column chromatography purification. Larger scale reactions were performed in an immersion-well apparatus under irradiation by a 125 W high-pressure mercury arc through Pyrex, while maintaining a nitrogen flux. In this case, the final purification was carried out by bulb to bulb distillation. In all cases, the purity of the extracted compounds was acceptable (>95%) for direct use or further chemical elaboration.

Photochemical synthesis of estragole 10 starting from 1c. A solution of **1c** (0.3 mmol), xanthone (1.5 mmol) and allyltrimethylsilane (15 mmol) in 30 ml of the chosen solvent was irradiated at 360 nm. The resulting mixture was purified by column chromatography (cycloexane–ethylacetate 99 : 1) or previously extracted with CH$_2$Cl$_2$ (in the case of the aqueous solvent) as described above and then purified.

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