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Photoinduced Three-Component Reaction: A Convenient Access to 3-Arylacetals or 3-Arylketals

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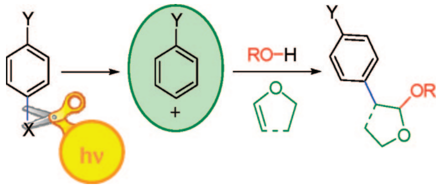
ABSTRACT

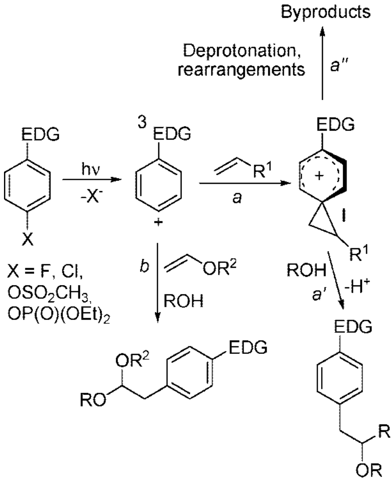


A mild and versatile method for the photoinduced three-component synthesis of 3-arylacetals and ketals is presented. Desired targets are smoothly obtained by irradiating aromatic halides or esters in alcohols, in the presence of vinyl ethers.

Multicomponent reactions (MCRs) are used in modern organic chemistry for the preparation of functionalized molecules by a cascade of chemical reactions.[1] Photoinduced MCRs are not common; one of the most representative examples is the nucleophile-olefin-combination-aromatic-substitution (NOCAS) process.[2a] This leads to a β-arylethyl ether starting from an arylnitrile, an olefin, and an alcohol (the solvent of the reaction). The key intermediates in this process are radical ions and further variations based again on such intermediates have been recently devised,[2b] but photochemistry makes accessible further highly activated intermediates potentially useful for three-component reactions.

Phenyl cations are electrophilic intermediates that are smoothly generated by photoinduced heterolytic cleavage of phenyl halides and esters.[3,4] We previously found that irradiation of these aromatics in the presence of alkenes and alcohols gave phenyl alkyl ethers through a three-component synthesis via a phenonium ion intermediate (**I**, Scheme 1, path *a*). Unfortunately, product mixtures are obtained because other processes compete efficiently with the desired reaction, namely, solvent addition onto **I** (path *a′*).[5] These are proton

Scheme 1. Competing Paths in the Arylation of Olefins



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(1) For an overview, see: *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.

(2) (a) Mangion, D.; Arnold, D. R. *Acc. Chem. Res.* **2002**, *35*, 297–304. (b) Lu, Z.-F.; Shen, Y.-M.; Yue, J.-J.; Hu, H.-W.; Xu, J.-H. *J. Org. Chem.* **2008**, *73*, 8010–8015.

(3) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713–721.

(4) Dichiarante, V.; Fagnoni, M. *Synlett* **2008**, 787–800.

10.1021/ol802560t CCC: $40.75

elimination and Wagner–Meerwein rearrangements (path *a″*) driving the adduct cation **I** to more stabilized intermediates (or products). On the other hand, it was demonstrated that when an n nucleophile such as an OH or COOH group is tethered to the alkene, a fast *intramolecular* attack onto carbocationic intermediate **I** is highly favored and a clean C–C, C–O tandem bond formation occurs. In this way, *β*-benzyl-lactones and tetrahydrofurans have been prepared.[4] This suggests that a selective three-component reaction could be obtained also in an *intermolecular* fashion, provided that the first formed adduct cation was stabilized in such a way that other competing reactions were disfavored and addition of the solvent predominated. It appeared reasonable that an oxonium ion[6] intermediate satisfied these requirements, and we surmised that addition of a phenyl cation onto a vinyl ether followed by alcohol trapping may lead to 3-arylacetals or 3-arylketals by the tandem formation of two new bonds, C–C and C–O (Scheme 1, path *b*).

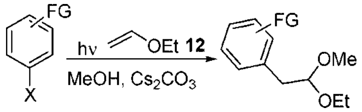
It should be noted that under these conditions *O*,*O*-mixed acetals may be obtained depending on the solvent chosen. This is an added bonus, because these derivatives have been exploited for preferential activation of the less hindered OR group (generally OMe) under Lewis acid catalysis. Examples are substitution by an alkynyl group in the synthesis of propargylic ethers[7] or by a 5-fluorouracil in the preparation of prodrugs.[8]

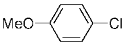
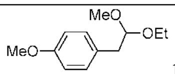
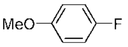
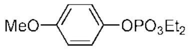
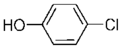
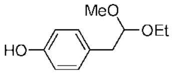
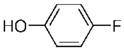
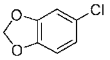
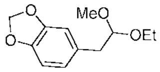
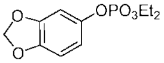
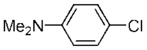
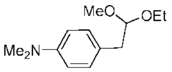
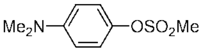
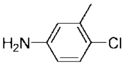
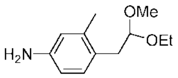
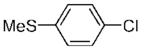
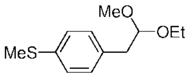
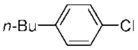
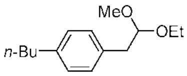
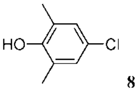
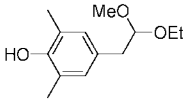
An explorative study was carried out to test the viability and the scope of the method. The results obtained by irradiating nitrogen flushed solutions of phenyl halides and esters **1**–**8** (0.05 M) in methanol in the presence of ethyl vinyl ether (**12**, 0.05 M) are reported in Table 1. Because of the liberation of mineral acids[4] in the photofragmentation and of the limited stability of acetals under such conditions, Cs_2CO_3 was added to the solution in an equimolar amount with respect to the aromatic substrates. This protocol allowed us to obtain good yields of the 3-aryl mixed acetals **15**–**22**.

In Table 1 the results obtained are grouped according to the target product. Thus, for the synthesis of 4-methoxyphenyl acetaldehyde ethyl, methyl acetal (**15**), three aromatic starting compounds were compared. 4-Chloroanisole (**1a**) turned out to be the most effective reagent and gave the acetal in 70% yield, whereas with 4-fluoroanisole (**1b**) and 4-methoxyphenyl diethyl phosphate (**1c**), the yields were lower and a longer irradiation time was required. With a lower amount of the trap (0.2 M), the arylacetal was obtained in a somewhat lower yield (53% vs 70%).

It is noteworthy that the hydroxyphenyl derivative **16** was obtained in a good yield from both 4-chlorophenol (**2a**) and 4-fluorophenol (**2b**) under comparable conditions, a remarkable result also because it was obtained starting directly from the phenols and skipping protection of the acidic OH group.

Table 1. Synthesis of 3-Arylacetals **15**–**22** by Irradiation of Aromatics **1**–**8** in the Presence of Ethyl Vinyl Ether (**12**)[a]



Ar-X	t_{irr} (h)	product, yield (%)
 **1a**	14	 **15**, 70 (53)[b]
 **1b**	60	**15**, 49
 **1c**	24	**15**, 45
 **2a**	14	 **16**, 70
 **2b**	14	**16**, 63 (85)[c]
 **3a**	14	 **17**, 62
 **3b**	30	**17**, 36
 **4a**	3	 **18**, 56 (40)[d]
 **4b**	8	**18**, 45
 **5**	4	 **19**, 56
 **6**	16	 **20**, 58
 **7**	14	 **21**, 56
 **8**	10	 **22**, 50

[a] Reaction conditions: ArX (0.05 M), **12** (0.5 M), and Cs_2CO_3 (0.025 M) irradiated in MeOH. [b] **12** (0.2 M). [c] **12** (1.0 M). [d] ArX (0.1 M).

Furthermore, compound **16** was formed from **2b** in a higher yield (85%) by using 1 M **12**. Compound **17**, containing two different acetal moieties, was prepared from chloride **3a** and, less satisfactorily, from phosphate **3b**.

N,*N*-Dimethylanilines **4a** and **4b** and aniline **5** likewise gave mixed acetals **18** and **19** in comparable yields and in a shorter irradiation time. Doubling the scale by using 0.1 M chloroaniline **4a** was possible with only a slight decrease of the yield of formation of arylacetal **18**. The scope of this procedure as far as the substituents were concerned was tested by the synthesis in reasonable yields of a 4-methylth-

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(5) See for instance: Protti, S.; Fagnoni, M.; Mella, M.; Albini, A. *J. Org. Chem.* **2004**, *69*, 3465–3473. Lazzaroni, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2007**, 4360–4365.

(6) These intermediates have been successfully used in total organic synthesis, e.g., for the preparation of cytotoxic Amphidinolides; see: Aïssa, C.; Riveiros, R.; Ragos, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512–15520. Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374–2375.

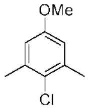
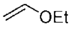
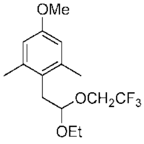
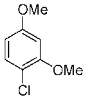
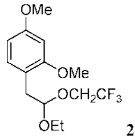
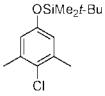
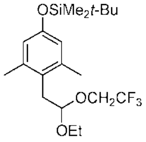
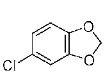
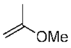
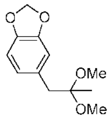
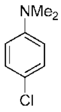
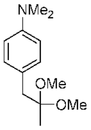
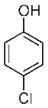
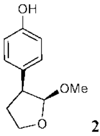
(7) Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1996**, *37*, 3819–3822.

(8) Saniger, E.; Campos, J. M.; Entrena, A.; Marchal, J. A.; Boulaiz, H.; Aránega, A.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **2003**, *59*, 8017–8026.

iophenyl (**20**) and a 4-butylphenyl (**21**) derivative. Dimethylated chlorophenol **8** likewise gave the *O*,*O*-mixed acetal **22**.

However, steric hindrance had some effect. Thus, a single methyl group in *ortho* with respect to the leaving group had no effect on the arylation, as shown by the efficient synthesis of acetal **19** from halide **5** in methanol. With *O,O′*-dimethyl phenyl chlorides such as **9** and **11**, as well as the 2,4-dimethoxyphenyl chloride **10**, poor arylation yields were obtained. In fact, under the above conditions the main process was reduction. However, the desired arylation was obtained when the reaction was carried out in 2,2,2-trifluoroethanol (TFE) rather than in methanol. In this case, mixed acetals were again obtained in yields comparable to those from nonhindered precursors (see Table 2). The use of such an ion stabilizing solvent allows the use of an easy removable base such as triethylamine (TEA). A more elaborated molecule such as **25**, where two functional groups are protected in an orthogonal manner, was smoothly synthesized. The extension of the method to the synthesis of α-arylacetone ketals was likewise tested by using 2-methoxypropene (**13**). The result was positive, and desired dimethyl ketals **26** and **27** were obtained when using 0.5 M of **13**, although a slight excess of base (0.03 M, Cs_2CO_3) was found to be required due to the lower stability of ketals with respect to acetals. Finally, the reaction of chlorophenol **1a** with 2,3-dihydrofuran (**14**) was explored. A fully regio- and stereoselective arylation occurred and afforded compound **28** as the *cis* diastereoisomer (de >98%).

Table 2. Photoinduced Synthesis of 3-Arylacetals and 3-Arylketals **23**−**28**[a]

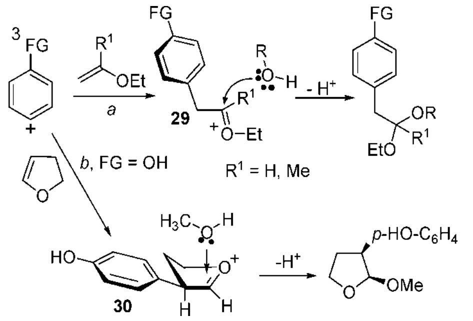
ArCl	vinyl ether	t_{irr} (h)	solvent, base	product, yield (%)
 **9**	 **12**	24	TFE, TEA	 **23**, 76
 **10**	**12**	36	TFE, TEA	 **24**, 41
 **11**	**12**	24	TFE, TEA	 **25**, 74
 **3a**	 **13**	14	MeOH, Cs_2CO_3[b]	 **26**, 59
 **4a**	**13**	2	MeOH, Cs_2CO_3[b]	 **27**, 66
 **1a**	 **14**	14	MeOH, Cs_2CO_3[b]	 **28**, 66

[a] Reaction conditions: ArX (0.05 M), **12**−**14** (0.5 M), Cs_2CO_3 (0.025 M) or TEA (0.05 M) irradiated in the chosen solvent. [b] Cs_2CO_3 (0.03 M).

The generation of triplet phenyl cations by photolysis of electron-rich aryl halides has been previously documented, both by experimental[3,4] and by computational[9,10] studies, as has the selective reaction of these intermediates with π nucleophiles.

The adduct cation undergoes intersystem crossing to the singlet state, making addition of the solvent (an n nucleophile) possible. The adduct is an oxonium ion, a relatively stabilized intermediate (see structure of **29**). The localization of the charge in **29** makes attack of the solvent at the β-carbon exclusive, in contrast to the two possible alternatives in phenonium intermediate **I** formed from simple alkenes (Scheme 1). Thus, in the present case attack by the solvent yields a single product, the desired 3-arylacetal (see Scheme 2).

Scheme 2. Proposed Mechanism of the Photoinduced Formation of 3-Arylacetals



The high 1,2-*cis* diastereoselectivity observed in the formation of compound **28** reasonably results from the preferred conformation of the intermediate tetrahydrofuran-derived oxonium ion **30**. The stereochemical outcome of the attack of a nucleophile onto this type of intermediates has been thoroughly studied by Woerpel and co-workers.[11] In our case, the selectivity appears to come from the "inside" attack[11] of the solvent onto conformer **30** where the aryl group is present in equatorial position.

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(9) Lazzaroni, S.; Dondi, D.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **2008**, *73*, 206–211.

(10) See for example: Protti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2008**, 2240–2247. Manet, I.; Monti, S.; Grabner, G.; Protti, S.; Dondi, D.; Dichiarante, V.; Fagnoni, M.; Albini, A. *Chem. Eur. J.* **2008**, *14*, 1029–1039.

(11) See for instance: Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747–8756. Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209. Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056–2064. Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063–2066.

Studies on further aromatic precursors and computational analyses aimed at confirming the hypotheses are in progress.

Apart from this issue, the above method allows the direct synthesis of 3-arylacetals and 3-arylketals, in turn useful intermediates, e.g., for the preparation of pyroglutamic acids[12] and of the anticancer agent omuralide[13] (by means of the Ugi reaction) and in combinatorial chemistry.[14] 3-Arylacetals(ketals) are usually prepared from precursors containing a preformed carbon skeleton by acid-catalyzed acetalization of the corresponding aldehydes and imines[14] or by the oxidation of styrenes catalyzed by Pd(II) complexes.[15] Recently, a Lewis acid mediated 1,2-migration of aryl groups in (1-alkoxy-2-iodoethyl)benzenes was also reported.[16] The preparation of these acetals through the formation of an aryl-C bond, however, is no trivial issue and involves two steps, the Pd-catalyzed addition of trimethylsilyl acetylene onto an aryl halide and the treatment with KOH in MeOH.[17]

The present method is appealing from the synthetic point of view, since it uses cheap starting compounds (aryl chlorides and vinyl ethers) under mild conditions (room temperature, no transition metal catalysis). In a single operation an aryl-C and a C-O bond are consecutively formed. Photohydrodehalogenation of the starting aromatic usually favored in alcoholic solvent take place to a minimal extent because vinyl ethers are excellent nucleophiles and readily trap the phenyl cation formed. Furthermore, the results show that aromatic derivatives not considered suitable for cross-coupling arylations such as phosphate esters[18] and especially fluorides[19] can be efficiently used. Finally, these reactions occur in alcohols, which are considered to be good solvents from a green synthetical chemistry point of view.[20]

Acknowledgment. Partial support of this work by MURST, Rome is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for compounds **3b** and **15−28**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802560T

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