Convenient synthesis of electron-donating substituted benzonitriles by photolysis of phenyl halides and esters†

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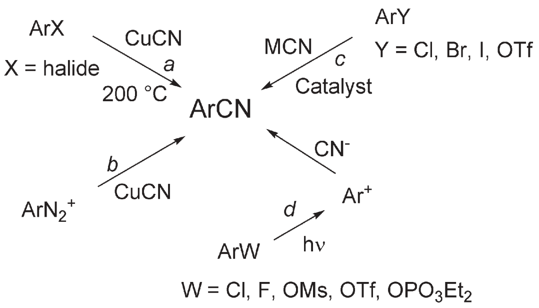
Irradiation of electron-donating substituted phenyl halides (fluorides and chlorides) or esters (mesylates, triflates and phosphates) in aqueous MeCN in the presence of KCN gives the corresponding benzonitriles in 48 to 100% yield through an ArS$_N$1 reaction with the intermediacy of a triplet phenyl cation.

Benzonitriles find large application as agrochemicals and pharmaceuticals. The classical preparations require a stoichiometric amount of copper(I) cyanide and form equimolar amounts of heavy metal waste as byproducts. These are the Rosenmund–von Braun reaction (Scheme 1, path *a*), usually carried out at a high (>150 °C) temperature, and the Sandmeyer reaction (path *b*), where the low stability of aryldiazonium salts is a limitation. Fortunately, the catalytic version of these reactions has been recently reported[1] and palladium-catalyzed cyanations[2] (path *c*) have been developed for many phenyl halides (mainly iodides or bromides) or esters (*e.g.* triflates).

However, several limitations remain, such as the cost of the Pd catalyst, the removal of the metal at the end of the reaction, the use of hazardous phosphine ligands and in some cases the poor reproducibility of the yields. Furthermore, the cyanide ion tends to deactivate the catalyst[3,4] and this fact introduces limitations on the choice of the solvent and cyanide source.[5]

A mild alternative for the synthesis of benzonitriles would be substituting light for the metal catalyst for activating Ar–X bonds. Indeed, a systematic study has shown that electron-donating substituted phenyl halides and esters undergo photoheterolysis in a polar medium and yield the corresponding phenyl cations (Ar$^+$) in the *triplet* state. The electronic distribution in this state makes it similar to a carbene rather than to a localized carbocation and leads to a peculiar reactivity. As an example, addition to π nucleophiles such as olefins and aromatics takes place selectively with little or no competition by solvents such as alcohols or water.[6,7]



Scheme 1 Pathways for the synthesis of benzonitriles.

We wondered whether these intermediates might be trapped by cyanide as well, thus opening a new path to benzonitriles (Scheme 1, path *d*).

Thus, we tested the photoreactivity of a series of phenyl halides or esters by irradiation (λ = 310 nm). A 1 : 3 (or 1 : 1) water–acetonitrile mixture was chosen as the solvent because it allowed the dissolution of both the organic reagent and of the cyanide source (KCN) and was thought to favor photoheterolysis of the precursor (compare ref. 7).

In the event, substitution of the nucleofugal group consistently took place and led indeed to benzonitriles in good to excellent yields with no competing formation of hydroxyphenyl derivatives (see Table 1 and Scheme 2).‡

As an example, 4-chloroaniline (**1a**, 0.01 M) gave 4-aminobenzonitrile (**9**) quantitatively (GC assessed) when irradiated for 15h in the presence of KCN 0.1 M. This product was obtained in 62% isolated yield after purification by column chromatography when starting from 0.05 M **1a**. A further concentration increase was impractical, because of competitive absorption by the benzonitrile formed, which progressively slowed down the conversion rate.

Interestingly, 4-fluoroaniline **1b** could be substituted for the chloro analogue **1a**, although a larger amount of KCN (0.3 M) was required in order to reach a satisfactory yield.[8] This involved shifting to a water–MeCN 1 : 1 mixture in order to have a homogeneous solution. On the other hand, photolysis of 4-bromo- and 4-iodoaniline gave 4-aminobenzonitrile in respectively 41 and 6% yield with the concomitant formation of aniline (20–30%, see Table 1). The poor results in the last case can be attributed to the increasing role of homolytic fragmentation with heavier halogens.[9]

The effect of changing the substituent position was then explored. Thus, 2-chloroaniline (**2a**) gave 2-aminobenzonitrile (**10**) in a 53% isolated yield, although not reaching complete consumption (90% in 40 h). Benzonitrile **10** was also formed from 2-fluoroaniline (**2b**), although in a low yield (22%). In contrast, the photocyanation reaction was unsatisfactory with 3-chloroaniline (**3**), and 3-aminobenzonitrile was formed in only 19% yield.

Tertiary amines were convenient precursors. 4-*N*,*N*-Dimethylaminobenzonitrile (**12**) was obtained starting both from 4-chloro-*N*,*N*-dimethylaniline and from the mesylate and phosphate esters of 4-*N*,*N*-dimethylaminophenol. In the first case a 93% yield was obtained with a 0.5 M cyanide concentration (with the more soluble Bu$_4$NCN replacing KCN). To our knowledge, this is the

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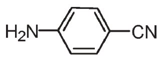
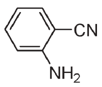
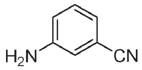
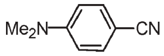
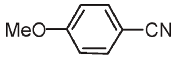
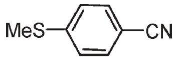
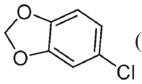
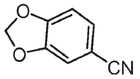
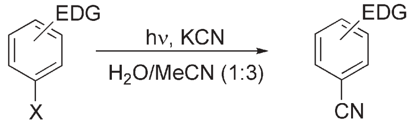
Table 1 Photoinduced synthesis of electron-donating substituted benzonitriles

Phenyl halide or ester (concentration/M)	KCN/M	Time/h	Benzonitrile	Yield[a] (%)
p-H_2N–C_6H_4–Cl (**1a**, 0.01)	0.1	15	 **9**	100 (62)[b]
p-H_2N–C_6H_4–F (**1b**, 0.05)	0.3[c]	17		71
p-H_2N–C_6H_4–Br (**1c**, 0.01)	0.1	22		41[d]
p-H_2N–C_6H_4–I (**1d**, 0.01)	0.1	22		6[e]
o-H_2N–C_6H_4–Cl (**2a**, 0.01)	0.3[c]	40	 **10**	53[b,f]
o-H_2N–C_6H_4–F (**2b**, 0.01)	0.1	18		22
m-H_2N–C_6H_4–Cl (**3**, 0.01)	0.3[c]	40	 **11**	19[b,f]
p-Me_2N–C_6H_4–Cl (**4a**, 0.01)	0.1	17	 **12**	57
p-Me_2N–C_6H_4–Cl (**4a**, 0.05)	0.5[g]	17		93
p-Me_2N–C_6H_4–OMs (**4b**, 0.025)	0.3[c]	17		56[b]
p-Me_2N–C_6H_4–PO_4Et_2 (**4c**, 0.01)	0.1	18		70
p-MeO–C_6H_4–Cl (**5a**, 0.01)	0.1	22	 **13**	90
p-MeO–C_6H_4–OMs (**5b**, 0.01)	0.1	24		48[h]
p-MeO–C_6H_4–OTf (**5c**, 0.01)	0.1	24		64[h]
p-HO–C_6H_4–Cl (**6a**, 0.01)	0.1	40	 **14**	54[i]
p-HO–C_6H_4–F (**6b**, 0.01)	0.1	24		69
p-MeS–C_6H_4–Cl (**7**, 0.01)	0.1	30	 **15**	53 (57)[b,j]
 (**8**, 0.05)	0.1	20	 **16**	77[b]

[a] GC yields. [b] Isolated yields, see ESI. [c] Water–MeCN 1 : 1 as the solvent. [d] Aniline (22%) was formed as a byproduct. [e] Aniline (31%) was formed as a byproduct. [f] Yields based on 90% consumed chloroaniline. [g] 4-Chloro-N,N-dimethylaniline (0.05 M) irradiated in the presence of Bu_4CN (0.5 M). [h] Reaction carried out in the presence of 0.9 M acetone, see text. [i] Phenol (12%) was also formed in the reaction. [j] Thioanisole (8%) was also isolated from the end mixture.

first example of the synthesis of a benzonitrile starting from an aryl phosphate. Indeed, the above aryl esters are cleanly converted into the nitriles by substitution of a sulfonate or phosphate group with no competing cleavage of the ArO–S or ArO–P bonds.

Application to other phenyl derivative bearing O- or S-bonded electron-donating substituents was likewise successful. Thus, both 4-chloroanisole or 4-methoxyphenyl mesylate and triflate gave 4-methoxybenzonitrile in excellent yield (up to 90%). Since the esters **5b** and **5c** did not absorb efficiently the wavelength range used, sensitization by acetone (0.9 M) was successfully adopted.



EDG = OH, OMe, OCH_2O, SMe, NH_2, NMe_2
X = Cl, F, OMs, OTf, OPO_3Et_2

Scheme 2 Preparation of benzonitriles by irradiation of phenyl halides or esters.

4-Chlorophenol was converted into 4-cyanophenol (**14**, 54%) accompanied by some phenol (12%). A cleaner reaction occurred with 4-fluorophenol, which gave compound **14** in 69% yield. The successful preparation of nitrile **14** directly from a 4-halophenol, avoiding the OH protection–deprotection sequence often required in metal mediated processes is noteworthy.

4-(Methylthio)benzonitrile was formed in 53% yield from 4-chlorothioanisole (**7**, 0.01 M). The yield was 57% when starting from 0.03 M **7** although some thioanisole (8%) was formed under these conditions.

5-Cyano-benzo[1,3]dioxole (77%, isolated yield) was obtained from chlorobenzodioxole (0.05 M) by using a moderate excess of KCN (0.1 M).

To summarize, a mild photoinduced cyanation reaction could be accomplished at room temperature starting from electron-rich phenyl halides and esters, which is complementary to the thermal reactions that are most effective with electron-poor derivatives.[2]

In the previous literature, there are sparse examples of introducing a cyano group by photonucleophilic substitution reactions.[10] These have been usually carried out at a low concentration ($<10^{-4}$ to 10^{-3} M). Various mechanisms have been proposed, including in one case a S_N1 mechanism.[11]

The present reaction clearly involves a unimolecular path (see again Scheme 1, path *d*).[12] In fact, the quantum yield of reaction of 4-chloroaniline (10^{-3} M) in water–acetonitrile 1 : 3 is $\Phi_r = 0.78$ and aniline is the only product.[13] The addition of KCN (from 10^{-3} M to 0.02 M) did not affect the overall quantum yield (Φ_r), while proportionally substituting the nitrile **9** for aniline. Likewise, 4-bromoaniline showed a $\Phi_r = 0.04$ virtually independent of the presence of KCN.

The results are in accordance with the formation of triplet phenyl cations as key intermediates, as expected from previous studies.[6,9,14] These species are either reduced in neat solvents or trapped by cyanide. With respect to our previous work, new phenyl cation precursors have been introduced, *viz*. 4-bromoaniline, 4-fluorophenol and 2-chloroaniline, while 4-iodo- and 3-chloroaniline have been shown to be unsuitable.[15]

The photochemical method can not compete with the metal mediated reactions in term of scope (the process being applicable only to the synthesis of electron-rich benzonitriles) and requires relatively dilute conditions (0.01 to 0.05 M). However, yields are good to excellent, although reduction may compete to some extent and this simple method offers some advantages. Thus, the use (and the disposal) of delicate and toxic metal catalysts are avoided and the mild conditions contrast with those required for the metal catalyzed cyanation of aryl chlorides (*e.g.* high temperature and the use of a pressure tube apparatus).[3,16] In contrast to the deactivation observed in the metal catalyzed process, the present reaction adequately tolerates the use of an excess of KCN, a relatively inexpensive cyanating agent. Indeed, the yields are generally improved by increasing the amount of cyanide ion. Furthermore, the photochemical method applies to precursors less susceptible to thermal reactions. As an example, phenyl chlorides and fluorides perform well here, while iodides and bromides are mostly used in the thermal syntheses. In particular, the thermal replacement of a fluoride with a cyano group met with some success only with derivatives strongly activated by electron-withdrawing groups.[17]

Likewise, phenyl esters, easily synthesized from the corresponding phenols, have been rarely used for thermal substitution by a cyano group,[18] while these give good results in the present reaction. This two step sequence results in the straightforward substitution of a CN for an OH group *via* the esters. The experimentally simple synthesis of benzonitriles presented here overcomes some drawbacks of the thermal reactions, such as the price of the catalyst and the removal of toxic metal waste. This advantage and the large scope should make it a viable synthetic alternative.

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Notes and references

‡ Photochemical synthesis of benzonitriles. General procedure. CAUTION: All the experiments must be carried out under a fume hood. The aqueous phase must be conveniently disposed of. A solution of compounds **1** to **8** (0.01–0.05 M), KCN (0.1–0.3 M) in a water–MeCN 1 : 3 (or 1 : 1) mixture in quartz tubes was flushed with nitrogen and irradiated in a multilamp reactor (310 nm, see ESI† for details). The final mixture was then analyzed by HPLC and the yields were determined by comparison with authentic samples of the benzonitriles. For preparative experiments (30 mL of solvent), acetonitrile was eliminated *in vacuo*, water was added and the mixture extracted with diethyl ether (in the synthesis of 4-cyanophenol acidification with HCl 0.1 M before extraction was required). The raw product was then purified by column chromatography (cyclohexane–ethyl acetate mixtures as the eluant). During the purification of aminobenzonitriles, NEt_3 (0.1%) was added to the eluant.

1 I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov and P. V. Petrovskii, *J. Organomet. Chem.*, 2004, **689**, 3810–3812; J. X. Wu, B. Beck and R. X. Ren, *Tetrahedron Lett.*, 2002, **43**, 387–389.

2 M. Sundermeier, A. Zapf and M. Beller, *Eur. J. Inorg. Chem.*, 2003, 3513–3526.

3 M. Sundermeier, A. Zapf, S. Mutyala, W. Baumann, S. Sans, S. Weis and M. Beller, *Chem. Eur. J.*, 2003, **9**, 1828–1836.

4 K. M. Marcantonio, L. F. Frey, Y. Liu, Y. Chen, J. Strine, B. Phenix, D. J. Wallace and C. Chen, *Org. Lett.*, 2004, **6**, 3723–3725.

5 M. Sundermeier, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 1661–1664.

6 M. Fagnoni and A. Albini, *Acc. Chem. Res.*, 2005, **38**, 713–721.

7 S. Protti, M. Fagnoni and A. Albini, *Org. Biomol. Chem.*, 2005, **3**, 2868–2871; M. De Carolis, S. Protti, M. Fagnoni and A. Albini, *Angew. Chem., Int. Ed.*, 2005, **44**, 1232–1236.

8 The presence of water is crucial for the photoreactivity of 4-fluoroaniline, see ref. 9.

9 M. Freccero, M. Fagnoni and A. Albini, *J. Am. Chem. Soc.*, 2003, **125**, 13182–13190.

10 For some examples see: M. Fagnoni and A. Albini, Photonucleophilic Substitution Reactions, in *Molecular and Supramolecular Photochemistry*, ed. V. Ramamurthy and K. Schanze, Dekker, New York, 2006, vol. 14, pp. 131–177.

11 M. B. Groen and E. Havinga, *Mol. Photochem.*, 1974, **6**, 9–21.

12 Notice that previous literature favors either an ArS_N2 pathway from the triplet state or photoionization giving the aromatic radical cation followed by addition of cyanide as the mechanism. As a matter of fact, however, literature data on the photocyanation reactions of electron-rich aromatic halides, *e.g.* of 4-chloroanisole, do fit an ArS_N1 mechanism and the Authors did not rule out this possibility. See for example: J. Den Heijer, O. B. Shadid, J. Cornelisse and E. Havinga, *Tetrahedron*, 1977, **33**, 779–786; K. Omura and T. Matsuura, *J. Chem. Soc. D*, 1969, 1394–1395; H. Lemmettyimen, J. Konijneberg, J. Cornelisse and C. A. G. O. Varma, *J. Photochem.*, 1985, **30**, 315–338. For a more detailed discussion of the unimolecular fragmentation of phenyl halides, see: S. Protti, M. Fagnoni, M. Mella and A. Albini, *J. Org. Chem.*, 2004, **69**, 3465–3473.

13 Water in the solvent mixture dramatically increases the reaction quantum yield (Φ_r) of 4-chloroaniline. Compare the present value with that reported in MeCN (0.44) or MeOH (0.50), see ref. 14.

14 B. Guizzardi, M. Mella, M. Fagnoni, M. Freccero and A. Albini, *J. Org. Chem.*, 2001, **66**, 6353–6363.

15 Triplet phenyl cations appear to be the most stable spin state when an electron-donating group is present in the *para* position (see ref. 9 and references cited therein). *ortho* and *meta* analogues are currently under investigation.

16 M. Sundermeier, A. Zapf, M. Beller and J. Sans, *Tetrahedron Lett.*, 2001, **42**, 6707–6710; F. Jin and P. N. Confalone, *Tetrahedron Lett.*, 2000, **41**, 3271–3273; R. K. Arvela and N. E. Leadbeater, *J. Org. Chem.*, 2003, **68**, 9125–9128.

17 See for example: M. Leibovitch, G. Olovsson, J. R. Scheffer and J. Trotter, *J. Am. Chem. Soc.*, 1998, **121**, 12755–12769; B. O. Patrick, J. R. Scheffer and C. Scott, *Angew. Chem., Int. Ed.*, 2003, **42**, 3775–3777; G. P. Ellis and T. M. Romney-Alexander, *Chem. Rev.*, 1987, **87**, 779–794.

18 Aryl mesylates and triflates has been used to some extent. See for example: A. Zhang and J. L. Neumeyer, *Org. Lett.*, 2003, **5**, 201–203; S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu and Q.-L. Zhou, *Org. Lett.*, 2005, **7**, 2333–2335; K. Takagi and Y. Sakakibara, *Chem. Lett.*, 1989, 1957–1958; V. Percec, J.-Y. Bae and D. H. Hill, *J. Org. Chem.*, 1995, **60**, 6895–6903.