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Photoredox-copper catalyzed Meerwein cyanoarylation of styrenes

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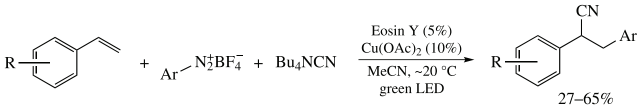
A new procedure for the cyanoarylation of styrenes with arenediazonium salts and Bu_4NCN employs double catalytic system Eosyn Y/$Cu(OAc)_2$ under the irradiation with green light (530 nm). In the case of diazonium salts bearing electron withdrawing substituents, the products are formed in 40–65% yields. The relative thiocyanatoarylation proceeds only in the presence of photocatalyst, but the $Cu(OAc)_2$ additive allows for the product yield improvement.



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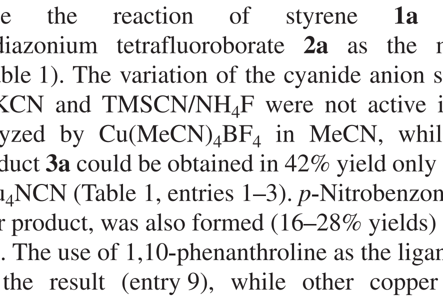
The goal of this work was to synthesize of 2,3-diarylpropanenitriles by cyanoarylation of styrenes. The Meerwein reaction provides a convenient method for alkene difunctionalization using diazonium salts.[1] Its exact mechanism has not been established yet, however a plausible mechanism (see Scheme S1 in Online Supplementary Materials) suggests the reduction of the diazonium salt to the corresponding aryl radical which undergoes addition to alkene forming secondary alkyl radical. As the reduction of the arenediazonium salt requires the presence of Cu^I salts and the Meerwein reaction employs Cu^{II} salts,[2] one can suppose that the Cu^I concentration is governed by the $Cu^{II} \Leftrightarrow Cu^I$ equilibrium ($E = -0.16$ eV). The aryl radical can also participate in the Sandmeyer reaction or can react with the olefin, thus the Meerwein synthesis demands the control over the aryl radical concentration, olefin excess and its ability to form enough stable secondary radical without tendency to polymerize. Further oxidation of the alkyl radical by Cu^{II} gives carbocation which can either eliminate β-proton to afford the arylation product of the initial olefin or react with a nucleophile giving the difunctionalization product. Due to such competition of two routes, one should control the substrate nature and the reaction conditions.[1(*a*),2]

During the last years the interest for the copper catalysis and redox catalysis (including photoredox reactions) drew the attention to the Meerwein reaction.[1(*a*),3] This process was applied to both intramolecular (formation of aryl substituted lactones)[4] and intermolecular[5] thiocyanatoarylation transformations as well as trifluoromethylthioarylation,[6] carboxyarylation,[7] and halogenoarylation[8] of alkenes. Though the key aryl radical can be generated *via* various routes (oxidation of arylboronic acids, carboxylic acids, sulfenates, reduction of halogenoarenes and aryl derivatives of polyvalent iodine[1(*a*),9]), we suppose that the easiest and cheapest access to aryl radicals is still the reaction of arenediazonium salts with copper salts (the Sandmeyer and Meerwein reactions).[1(*b*)] To our surprise, until now no literature data can be found on the olefin cyanoarylation using diazonium salts. The only exclusion is the reaction between arenediazonium salt and 1,3-butadiene catalyzed by CuCN in the presence of KCN which afforded 1,4-cyanoarylation product in 20–30% yields.[10]

We chose the reaction of styrene **1a** with 4-nitrophenyldiazonium tetrafluoroborate **2a** as the model (Scheme 1, Table 1). The variation of the cyanide anion source showed that KCN and $TMSCN/NH_4F$ were not active in the reaction catalyzed by $Cu(MeCN)_4BF_4$ in MeCN, while the Meerwein product **3a** could be obtained in 42% yield only in the presence of Bu_4NCN (Table 1, entries 1–3). *p*-Nitrobenzonitrile, the Sandmeyer product, was also formed (16–28% yields) along with polymers. The use of 1,10-phenanthroline as the ligand did not improve the result (entry 9), while other copper salts decreased the yield of the target product (entries 3, 4). However, the application of $Cu(OAc)_2$ gave compound **3a** in 47% yield and diminished twice the yield of *p*-nitrobenzonitrile (entry 5). The introduction of the ligand into the catalytic system (entry 7), irradiation of the reaction mixture with blue light, diminishing the catalyst loading (entry 5) did not further improve the result. Styrene polymerization remained the main side process, which can be explained by high concentration of aryl radical formed. Indeed, with rapid addition of the diazonium salt neither Meerwein, nor Sandmeyer products were formed. On the contrary, the desired reaction took place when diazonium salt was added slowly dropwise to the cooled solution of olefin and



Scheme 1 *Reagents and conditions*: i, catalyst, MeCN, room temperature (see Tables 1 and 2).

Table 1 Cu-catalyzed cyanoarylation of styrene **1a**.[a]

Entry	Catalyst	‘CN⁻’	Product yields (%)		
			3a	$4\text{-}O_2NC_6H_4CN$	$PhNO_2$
1	$Cu(MeCN)_4BF_4$	KCN	10 (traces[b])	5	–
2	$Cu(MeCN)_4BF_4$	Bu_4NCN	42	28	–
3	CuCN (or CuI)	Bu_4NCN	33 (24)	16 (16)	0 (5)
4	$Cu(BF_4)_2$	Bu_4NCN	33	13	–
5	$Cu(OAc)_2$	Bu_4NCN	47 (43,[c] 41,[d] 46[e])	14 (7,[c] 9,[d] 8[e])	9 (8,[c] 5,[d] 11[e])
6[f]	$Cu(OAc)_2$	Bu_4NCN	traces	–	–
7	$Cu(OAc)_2$/Phen (10%)	Bu_4NCN	42	5	8
8[f]	$Cu(OAc)_2$/Phen (10%)	Me_3SiCN	6	–	6
9	$Cu(MeCN)_4BF_4$/Phen (10%)	Bu_4NCN	43	23	–
10[g]	$Cu(MeCN)_4BF_4$/Phen (6%)	Me_3SiCN	75	–	–

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (0.3 mmol), cyanide source (0.36 mmol), catalyst (10 mol%), MeCN (3 ml), ~20 °C, 8 h. [b] With Me_3SiCN and NH_4F (0.6 mmol each) instead of Bu_4NCN. [c] The reaction was performed under blue LED irradiation (450 nm). [d] 5 mol% $Cu(OAc)_2$ was used. [e] Diazonium salt was slowly syringed for 1 h. [f] *p*-Nitroaniline and Bu^tONO (0.45 mmol each) were used instead of **2a**. [g] Reaction conditions: *p*-nitroanilne and Bu^tONO (0.9 mmol each), **1a** (0.3 mmol), Me_3SiCN (0.6 mmol), catalyst (5 mol%), MeCN (3 ml), ~20 °C, 8 h.

cyanide. However, slower addition using a syringe pump did not improve the yield (entry 5). To further diminish the concentration of aryl radical, we tried the reaction with the diazonium salt obtained *in situ* from aniline and Bu^tONO (entry 6), but product **3a** was formed only in trace amounts. The change of Bu_4NCN for Me_3SiCN was also unsuccessful (entry 8). This result seems to be strange enough because it had been reported that the reactions gave 78% yield using Me_3SiCN in the presence of Cu^I complex,[11] and this result was verified by us (entry 10). Obviously, the reaction outcome is sensitive to any factor, which needs further clarification (*cf.* ref. 12).

To improve the yield of product **3a**, we carried out photoredox-catalyzed reaction using various photosensitizers under the irradiation with visible light (Table 2, for the full data and photosensitizer structures, see Online Supplementary Materials).

Successful application of this reaction was previously described for the Meerwein addition using the following nucleophiles: alcohols,[13] enol ethers,[14] thiocyanates,[15] acetonitrile,[16] DMF,[17] and even electron rich arenes.[18] Intramolecular reaction of this type was employed for the synthesis of heterocyclic systems.[19] However, the cyanoarylation using Ru^{II} and Ir^{III} complexes and Eosin Y as photocatalysts did not lead to the desired product but rather only polymerization occurred (Table 2, entries 1, 2, 5). The application of copper salts and photocatalysts (dual catalysis) was studied using various Cu^I and Cu^{II} salts in the presence of Ru^{II} and Ir^{III} complexes or different organic photosensitizers. The majority of experiments did not improve the result which was obtained with $Cu(OAc)_2$, but the combination of $Cu(OAc)_2/Ru(bpy)_3(PF_6)_2$ provided the 57% yield of the Meerwein product **3a** without the formation of the Sandmeyer product (entry 1). The combination $Cu(OAc)_2$/Eosin Y afforded 65% of compound **3a** and only 5% yield of the Sandmeyer *p*-nitrobenzonitrile (entry 5). Thus, it was found possible to achieve good yield and chemoselectivity, however the polymerization could not be fully suppressed.

Table 2 Photoredox-copper catalyzed cyanoarylation of styrene **1a**.[a]

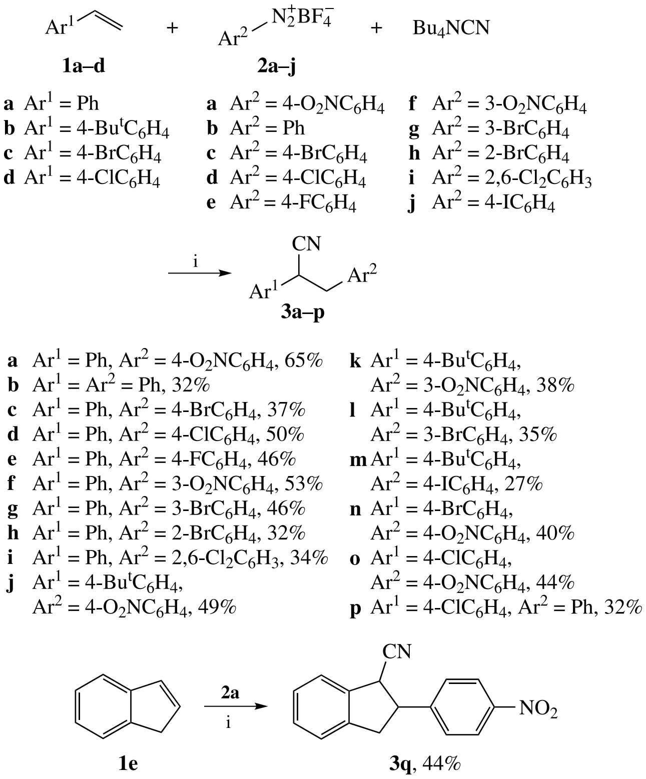
Entry	Photocatalyst (mol%)	Product yields (%)	
		3a	$4\text{-}O_2NC_6H_4CN$
1	$Ru(bpy)_3(PF_6)_2$ (2)[b]	57 (0,[c] 29,[d] 45[e])	0 (0,[c] 15,[d] 20[e])
2	$Ir(ppy)_3$ (2)[b]	41 (0[c])	6 (0[c])
3	$Ir(ppy)_2(dtbbpy)$ (2)[b]	48	7
4	$Ru(Phen)_3(PF_6)_2$ (2)[b]	31	4
5	Eosin Y (5)[f]	65 (0[c])	5 (0[c])
6	Rodamine 6G (5)816[f]	45	8
7	Rose Bengal (5)[f]	37	9
8	Eosin B (5)[f]	41	8
9	4Cztpn (5)[f]	42	12
10	10-Me-9-MesAcr (5)[b]	43	10

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (0.3 mmol), cyanide source (0.36 mmol), photocatalyst (2–5 mol%), $Cu(OAc)_2$ (10 mol%), MeCN (3 ml), ~20 °C, LED irradiation, 8 h. [b] The reaction was performed under blue LED irradiation (450 nm). [c] Without $Cu(OAc)_2$. [d] CuCN (10 mol%) instead of $Cu(OAc)_2$ was used. [e] $Cu(MeCN)_4BF_4$ (10 mol%) instead of $Cu(OAc)_2$ was used. [f] The reaction was performed under green LED irradiation (530 nm).

Under optimized conditions, the reaction with diazonium salts **2a–j** and substituted styrenes **1a–e** gave nitriles **3a–q** (Scheme 2, 17 examples, 27–65% yields).[†] The analysis of the results demonstrates that the successful processing demands the presence of electron withdrawing substituents in the diazonium salts **2** (the best is nitro group). As for styrenes, the most reactive is parent styrene **1a**, while the yields in cases of substituted analogues **1b–d** are somewhat lower. Anyway, this procedure seems suitable for the synthesis of nitroarenes of new promising chemotypes (*cf.* ref. 20).

Though the synthetic result of this reaction can be assessed as satisfactory, the behaviour of the cyanide anion still cannot be explained. Since the thiocyanatoarylation reaction is most relevant to our case among known processes of this type,[15] it was tested under the photoredox conditions (Scheme 3). The coupling of reactants **1a** and **2a** in the presence of $Ru(bpy)_3(PF_6)_2$ and visible light irradiation gave 55% of the target thiocyanate **4**. However, in the presence of $Cu(OAc)_2$ the Meerwein product **4** was not formed, and only the Sandmeyer product, $4\text{-}O_2NC_6H_4SCN$, was obtained in 70% yield. Meawhile, the combination of the photoredox catalyst and $Cu(OAc)_2$ provided 72% yield of **4** along with small amount (14%) of $4\text{-}O_2NC_6H_4SCN$.

[†] *Cyanoarylation of styrenes with diazonium salts (general procedure).* A Schlenk tube equipped with magnetic stirrer was charged with Eosin Y (10 mg, 0.015 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (6 mg, 0.03 mmol), capped with a rubber septum and filled with dry argon, and deaerated MeCN (1 ml) was syringed. Styrene **1** (1.2 mmol, 4 equiv.) and Bu_4NCN (96 mg, 0.36 mmol, freshly prepared solution in 1 ml of deaerated MeCN) were consequently syringed. The mixture was cooled to 0 °C in ice bath, and freshly prepared solution of arenediazonium salt **2** (0.3 mmol) in deaerated MeCN (1 ml) was added drop by drop within 1 min. The vessel was then placed in the photoreactor (see Online Supplementary Materials, Figure S1), and the mixture was stirred at room temperature under green light irradiation for 8 h. The mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane and subjected to column chromatography on silica gel using petroleum ether/dichloromethane mixtures as eluents.



1a–d **2a–j**

a $Ar^1 = Ph$
b $Ar^1 = 4\text{-}Bu^tC_6H_4$
c $Ar^1 = 4\text{-}BrC_6H_4$
d $Ar^1 = 4\text{-}ClC_6H_4$

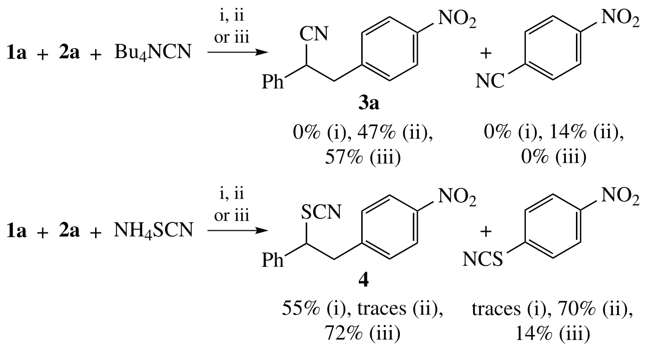
a $Ar^2 = 4\text{-}O_2NC_6H_4$
b $Ar^2 = Ph$
c $Ar^2 = 4\text{-}BrC_6H_4$
d $Ar^2 = 4\text{-}ClC_6H_4$
e $Ar^2 = 4\text{-}FC_6H_4$
f $Ar^2 = 3\text{-}O_2NC_6H_4$
g $Ar^2 = 3\text{-}BrC_6H_4$
h $Ar^2 = 2\text{-}BrC_6H_4$
i $Ar^2 = 2,6\text{-}Cl_2C_6H_3$
j $Ar^2 = 4\text{-}IC_6H_4$

3a–p

a $Ar^1 = Ph$, $Ar^2 = 4\text{-}O_2NC_6H_4$, 65%
b $Ar^1 = Ar^2 = Ph$, 32%
c $Ar^1 = Ph$, $Ar^2 = 4\text{-}BrC_6H_4$, 37%
d $Ar^1 = Ph$, $Ar^2 = 4\text{-}ClC_6H_4$, 50%
e $Ar^1 = Ph$, $Ar^2 = 4\text{-}FC_6H_4$, 46%
f $Ar^1 = Ph$, $Ar^2 = 3\text{-}O_2NC_6H_4$, 53%
g $Ar^1 = Ph$, $Ar^2 = 3\text{-}BrC_6H_4$, 46%
h $Ar^1 = Ph$, $Ar^2 = 2\text{-}BrC_6H_4$, 32%
i $Ar^1 = Ph$, $Ar^2 = 2,6\text{-}Cl_2C_6H_3$, 34%
j $Ar^1 = 4\text{-}Bu^tC_6H_4$, $Ar^2 = 4\text{-}O_2NC_6H_4$, 49%
k $Ar^1 = 4\text{-}Bu^tC_6H_4$, $Ar^2 = 3\text{-}O_2NC_6H_4$, 38%
l $Ar^1 = 4\text{-}Bu^tC_6H_4$, $Ar^2 = 3\text{-}BrC_6H_4$, 35%
m $Ar^1 = 4\text{-}Bu^tC_6H_4$, $Ar^2 = 4\text{-}IC_6H_4$, 27%
n $Ar^1 = 4\text{-}BrC_6H_4$, $Ar^2 = 4\text{-}O_2NC_6H_4$, 40%
o $Ar^1 = 4\text{-}ClC_6H_4$, $Ar^2 = 4\text{-}O_2NC_6H_4$, 44%
p $Ar^1 = 4\text{-}ClC_6H_4$, $Ar^2 = Ph$, 32%

1e **3q**, 44%

Scheme 2 *Reagents and conditions*: i, **1** (4 equiv.), **2** (1 equiv.), Bu_4NCN (1.2 equiv.), Eosin Y (5 mol%), $Cu(OAc)_2$ (10 mol%), green LED, MeCN, ~20 °C, 8 h.



3a

0% (i), 47% (ii), 57% (iii)

0% (i), 14% (ii), 0% (iii)

4

55% (i), traces (ii), 72% (iii)

traces (i), 70% (ii), 14% (iii)

Scheme 3 *Reagents and conditions*: i, **1a** (4 equiv.), **2a** (1 equiv.), Bu_4NCN or NH_4SCN (1.2 equiv.), $Ru(bpy)_3(PF_6)_2$ (2 mol%), blue LED, MeCN, ~20 °C, 8 h; ii, the same as i, with $Cu(OAc)_2$ (10 mol%); iii, the same as i, with $Ru(bpy)_3(PF_6)_2$ (2 mol%) and $Cu(OAc)_2$ (10 mol%).

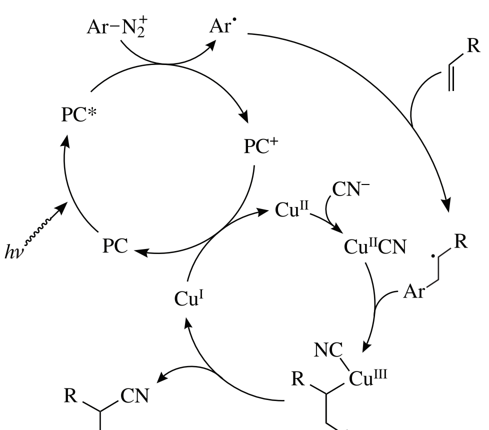


Figure 1 Proposed mechanism of photoredox-copper catalyzed Meerwein cyanoarylation of styrenes (PC is photocatalyst).

The question why cyanide and thiocyanate anions behave so differently is still open. We suppose that the very combination of the photoredox catalyst and Cu^{II} salt provides favorable concentrations of aryl radical and Cu^{II} for the formation of the Meerwein product. The suggested mechanism of photoredox-copper catalyzed Meerwein cyanoarylation is outlined in Figure 1.

To conclude, we have to emphasize an unusual behaviour of cyanide anion in the Meerwein cyanoarylation of styrenes and importance of the combination of the photoredox catalysis with Cu^{II} salts catalysis for the successful synthesis of the double addition products in yields from moderate to good.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.015.

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