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ARYL RADICALS BY COPPER(II) OXIDATION OF HYDRAZINES: A NEW METHOD FOR THE OXIDATIVE AND REDUCTIVE ARYLATION OF ALKENES

Teresa Varea, Maria E. González-Núñez, Javier Rodrigo-Chiner,
and Gregorio Asensio*
Departamento de Química Orgánica. Facultad de Farmacia.
Universidad de Valencia. Avda. Blasco Ibáñez, 13
E-46010-Valencia, Spain

ABSTRACT: A new source of aryl radicals interesting from the preparative point of view has been found in the reaction of arylhydrazines and copper(II) sulfate. *The process allows selectively both the* reductive and oxidative arylation of alkenes.

The development of new methods for C-C bond formation using radicals has attracted great attention in the last few years. While many sources of alkyl radicals have been found and used successfully in organic synthesis the scope of this methodology applied to aryl radicals is much more limited[1]. The most common methods used for the preparative generation of aryl radicals are the reduction with tributyltin hydride, or the light induced dehalogenation, of aryl halides (equations 1 and 2)[1], and the copper(I) promoted decomposition of aryldiazonium ions in the presence of alkenes (equation 3) in the so-called Meerwein reaction[2] which allows the preparation of oxidative arylation products (formal addition of Ar-Cl to the alkene). The methods involving aryl halide lead to reductive arylation of olefins (formal addition of Ar-H) and this has been also achieved in the reduction of diazonium salts by Ti(III) salts[3] (equation 4).

$$\mathrm{ArHal} + \mathrm{CH_2{=}CHZ} \xrightarrow{\mathrm{Bu_3SnH}} \mathrm{ArCHCHZ} \qquad (1)$$

$$\mathrm{ArHal} + \mathrm{CH_2{=}CHZ} \xrightarrow{h\nu} \mathrm{ArCH_2CH_2Z} \qquad (2)$$

$$\mathrm{ArN_2^+\ Hal^-} + \mathrm{CH_2{=}CHZ} \xrightarrow{\mathrm{Cu(I)}} \mathrm{ArCH_2CH(Hal)Z} \qquad (3)$$

$$\mathrm{ArN_2^+\ Hal^-} + \mathrm{CH_2{=}CHZ} \xrightarrow{\mathrm{Ti(III)}} \mathrm{ArCH_2CH_2Z} \qquad (4)$$

No method has been available so far to effect the reductive or the oxidative arylation based *on a single procedure. We wish to report now our results on the reaction of* arylhydrazines (1) with different copper(II) salts (2) and an alkene (3) to afford alternatively products resulting from the oxidative (4) or reductive (5) arylation of the C=C double bond (scheme 1). The efficiency of this C-C bond formation process depends on the substitution patterns of the starting hydrazine and alkene (see table 1).

Scheme 1

$$\underset{\underline{1}}{R\text{-}C_6H_4NHNH_2} + \underset{\underline{2}}{3Cu(II)X_n} + \underset{\underline{3}}{5CH_2{=}CHZ} \longrightarrow \underset{\underline{4}\text{ or }\underline{5}}{R\text{-}C_6H_4\text{-}CH_2CHYZ} + \underset{\underline{6}\text{ or }\underline{7}}{R\text{-}C_6H_4\text{-}Y} + Cu(I)X$$

R	
p-NO_2	**1a**
p-Br	**1b**

n	X	
2	Cl	**2a**
2	Br	**2b**
1	SO_4	**2c**

Z	
CN	**3a**
CO_2Me	**3b**

R	Y	Z	
p-NO_2	Cl	CN	**4a**
p-NO_2	Br	CN	**4b**
p-NO_2	Cl	CO_2Me	**4c**
p-NO_2	Br	CO_2Me	**4d**
p-NO_2	H	CN	**5a**
p-NO_2	H	CO_2Me	**5b**
p-Br	H	CN	**5c**
p-Br	H	CO_2Me	**5d**

R	Y	
p-NO_2	Cl	**6a**
p-NO_2	Br	**6b**
p-NO_2	H	**7a**
p-Br	H	**7b**

TABLE 1 (see scheme 1)

Hydrazine	Copper salt	Alkene	Products (Yield%)	
1a	**2a**	**3a**	**4a**(22)	**6a**(70)
1a	**2c**[a)]	**3a**	**4a**(27)	**6a**(60)
1a	**2b**	**3a**	**4b**(30)	**6b**(60)
1a	**2c**[b)]	**3a**	**4b**(48)	**6b**(35)
1a	**2a**	**3b**	**4c**(29)	**6a**(59)
1a	**2c**[a)]	**3b**	**4c**(35)	**6a**(54)
1a	**2b**	**3b**	**4d**(41)	**6b**(50)
1a	**2c**[b)]	**3b**	**4d**(47)	**6b**(42)
1a	**2c**	**3a**	**5a**(46)	**7a**(22)
1a	**2c**	**3b**	**5b**(55)[c)]	-
1b	**2c**	**3a**	**5c**(85)	**7b**(10)
1b	**2c**	**3b**	**5d**(90)[d)]	-

[a)] 5 equivalents of NaCl were used mixed with **2c**. [b)] 5 equivalents of NaBr were used mixed with **2c**. [c)] 30% of $ArCH_2CH(CO_2Me)CH_2CH_2CO_2Me$ is obtained as side product. [d)] 5% of $ArCH_2CH(CN)CH_2CH_2CN$ is obtained as side product.

We believe that the reaction of aryl hydrazines **1** with copper(II) salts **2** gives rise to the formation of aryl radicals (**8**) (equations 5-9) which fate depends on the reaction conditions employed.

$$\mathrm{ArNHNH_2} + \mathrm{Cu(II)} \longrightarrow (\mathrm{ArNHNH_2})^{+\bullet} + \mathrm{Cu(I)} \tag{5}$$

$$(\mathrm{ArNHNH_2})^{+\bullet} \longrightarrow (\mathrm{ArNHNH})^{\bullet} + \mathrm{H}^{+} \tag{6}$$

$$(\mathrm{ArNHNH})^{\bullet} + \mathrm{Cu(II)} \longrightarrow (\mathrm{ArNHNH})^{+} + \mathrm{Cu(I)} \tag{7}$$

$$(\mathrm{ArNHNH})^{+} \longrightarrow \mathrm{ArN{=}NH} + \mathrm{H}^{+} \tag{8}$$

$$\mathrm{ArN{=}NH} \longrightarrow \underset{\underline{\mathbf{8}}}{\mathrm{Ar}^{\bullet}} + \mathrm{N_2} + \mathrm{H}^{\bullet} \tag{9}$$

Three different copper(II) salts have been tested: chloride (**2a**) bromide (**2b**), and sulfate (**2c**). In all cases the aryl hydrazine is rapidly oxidized to the corresponding aryl radical. When copper(II) halides are used this radical follows a reaction pathway similar to that proposed by Kochi[4] for reactions of aryl radicals when derived from diazonium salts under Meerwein's conditions[5,6]. This radical reacts regioselectively with the terminal carbon of the alkene to give a radical intermediate (**9**) (equation 10), which reacts with the copper(II) halide and a ligand transfer takes place to afford the corresponding oxidative arylation product (**4**) (equation 11). Conversely, when copper(II) sulfate is used, the ligand transfer reaction does not occur and the intermediate radical (**9**) abstracts an hydrogen after most probably from the unreacted hydrazine or some of its intermediate oxidized forms (equation 12). Consequently, the reductive arylation products (**5**) are readily obtained in this case. Aryl halides appear as side products when a copper(II) halide is present in the medium, and this decreases the yield in alkene arylation. This side reaction is also found in the usual Meerwein's arylation procedure[2a] and takes place by ligand transfer from the copper(II) halide to the aryl radical[5] (Sandmeyer reaction). In a similar way, in the reactions with copper(II) sulfate the abstraction of $\mathrm{H}^{\bullet}$ by the radical from the hydrazine or its intermediate oxidized forms leads to the corresponding reduced aromatic compound (equations 13 and 14).

$$\underset{\underline{\mathbf{8}}}{\mathrm{Ar}^{\bullet}} + \mathrm{CH_2{=}CHZ} \longrightarrow \underset{\underline{\mathbf{9}}}{\mathrm{ArCH_2CH^{\bullet}Z}} \tag{10}$$

$$\mathrm{ArCH_2CH^{\bullet}Z} + \mathrm{Cu(II)Hal}_n \longrightarrow \underset{\underline{\mathbf{4}}}{\mathrm{ArCH_2CH(Hal)Z}} \tag{11}$$

$$\mathrm{ArCH_2CH^{\bullet}Z} \xrightarrow{\mathrm{H^{\bullet}\,abstraction}} \underset{\underline{\mathbf{5}}}{\mathrm{ArCH_2CH_2Z}} \tag{12}$$

$$\mathrm{Ar}^{\bullet} + \mathrm{Cu(II)Hal}_n \longrightarrow \underset{\underline{\mathbf{6}}}{\mathrm{ArHal}} \tag{13}$$

$$\mathrm{Ar}^{\bullet} \xrightarrow{\mathrm{H^{\bullet}\,abstraction}} \underset{\underline{\mathbf{7}}}{\mathrm{ArH}} \tag{14}$$

When an excess of sodium chloride or bromide is added to the reaction mixture in oxidations performed with copper(II) sulfate, only oxidative arylation products (**4**) are obtained, the hydrogen abstraction process being inhibited. The use of the mixture copper(II) sulfate/sodium halide is advantageous over the direct use of the corresponding copper(II) salt in the synthesis of oxidative arylation products (**4**), since the trapping of the aryl radical by the copper(II) halide occurs to a lesser extent. Three mole of copper(II) salt react with each mol of aryl hydrazine. Experiments carried out using a 2:1 copper(II) to hydrazine ratio gave decreased yields in arylation products and gave side reactions such as self-coupling of the aryl radicals, formation of azocompounds, and hydrogen abstraction from the unreacted or partially oxidized hydrazine. Reactions were carried out in a 3:1 acetic acid-water mixture that affords a homogeneous reaction medium. Reactions in two phases gave decreased yields of arylation products **4** and **5**.

The reactions of copper(II) sulfate with aryl hydrazines have a particular interest a new sources of aryl radicals from the preparative point of view since they allow both the oxidative and reductive arylation of alkenes as desired.

Typical Experimental Procedure.

To a 1:1 acetic acid/water mixture (20ml), copper(II) sulfate (4.79g, 30 mmol) and methyl acrylate (4.5ml, 50mmol) are added. Over this mixture arylhydrazine **1a** (1.53g, 10mmol) disolved in acetic acid (20ml) is added dropewise with vigorous stirring. Nitrogen evolution occurs, the colour of the solution changes from blue to greenish and a solid precipitates. After one hour the solid is removed by filtration, and the resulting solution is extracted with ether, the organic layer washed with 2N sodium hydroxide, dried over sodium sulfate and evaporated to yield a solid residue (2.1g). The residue is chromatographed on silicagel with a mixture of hexane and ethyl acetate (5:1) to give methyl 3-(*p*-nitrophenyl)-propanoate **5b** (1.15g, 55%) and methyl 3-carboxymethyl-5-(*p*-nitrophenyl)-pentanoate (0.88g, 30%).

All the products were identified by ^{1}Hnmr, ^{13}Cnmr and mass spectrometric analysis.

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