Synthetic Methods

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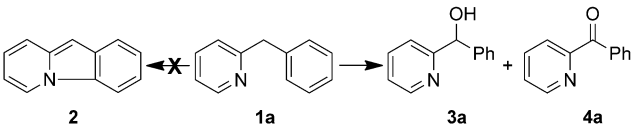
Synthesis of Aryl(di)azinyl Ketones through Copper- and Iron-catalyzed Oxidation of the Methylene Group of Aryl(di)azinylmethanes**

*Johan De Houwer, Kourosch Abbaspour Tehrani, and Bert U. W. Maes**

Aryl(di)azinyl ketones are very useful intermediates in the synthesis of pharmaceuticals, such as antihistamines, antimalarials, antiarrhythmic agents, β_2-adrenergic agonists, and anticancer therapeutics.[1] The oxidation of aryl(di)azinylmethanes is an attractive approach to synthesize these compounds. Classical conditions for this transformation often apply (more than) stoichiometric quantities of hazardous oxidants, such as potassium permanganate and selenium dioxide.[2] In the context of the current drive for a more sustainable society, in which waste minimization and atom economy are of utmost importance, the development of sustainable and inexpensive oxidation protocols is highly desirable. A lot of effort has already been made in rendering oxidative processes catalytic by utilizing transition metals in combination with cheaper oxidants, such as peroxides and molecular oxygen.[3,4] Also, the use of nonmetal-based catalysts has been investigated over the last decade.[5] However, some of these protocols suffer from poor selectivity and require harsh reaction conditions, expensive catalysts, or the use of a large excess of less sustainable oxidants, such as peroxides. Herein, we report a transition metal catalyzed oxidation of aryl(di)azinylmethanes by using cheap and readily available base metals (Cu and Fe) as catalysts in combination with O_2, the most sustainable oxidant available.[6]

Recently, our research group has reported a Cu-catalyzed intramolecular C-H amination of *N*-phenylpyridin-2-amine for the synthesis of the pyrido[1,2-*a*]benzimidazole skeleton.[7] Surprisingly, in an attempt to synthesize pyrido[1,2-*a*]indole (**2**) starting from 2-benzylpyridine (**1a**) that was based on this method, a mixture of phenyl(pyridin-2-yl)methanol (**3a**) and phenyl(pyridin-2-yl)methanone (**4a**) was obtained instead (Scheme 1).



Scheme 1. Initial reaction that revealed the oxidation method. Conditions: $Cu(OAc)_2{\cdot}H_2O$ (15 mol%), AcOH (5 equiv), DMSO, O_2, 100 °C, 24 h.

This unexpected result prompted us to optimize the reaction conditions for the benzylic oxidation of **1a**. 10 mol% of $Cu(OAc)_2{\cdot}H_2O$ is the optimal catalyst loading (Table 1, entries 1–3). Omitting the Cu catalyst gave only traces of the desired product (Table 1, entry 4), thus showing the necessity of the catalyst. Next we turned our attention to the source of Cu; Cu halide salts gave faster reactions than the other Cu sources that were assessed (Table 1, entries 5–10). The difference between the Cu^I and Cu^{II} salts was negligible, which suggests that the reaction proceeds via a Cu^{II} species and that the Cu^I salts are oxidized in situ. The appearance of the typical green-blue color of Cu^{II} at the beginning of the reaction supports this hypothesis. It should be highlighted that even Cu metal can be used to promote the oxidation (Table 1, entry 6). To test whether Cu or impurities of other metals that are present are responsible for the catalysis, a very pure sample of CuI (99.999%) was tested; this gave essentially the same result as with 98% grade CuI (Table 1, entry 11). CuI (98%) was chosen as the ideal catalyst precursor based on a combination of a fast conversion of the substrate and the best price/mol ratio of all of the tested copper halides. From the solvents that were tested, DMSO gave the fastest reaction (Table 1, entries 12–14) and was, therefore, selected for the rest of the optimization study. Finally the influence of the additive was investigated. Lowering the amount of acetic acid from five to only one equivalent led to a much slower reaction, whereas the ketone/alcohol ratio (selectivity) improved (compare Table 1, entries 10 and 15). A control experiment without additive revealed that the use of an acid additive is vital for the oxidation process (Table 1, entry 16). When pivalic acid was used, a similar result was obtained (Table 1, entry 17). With benzoic acid and trifluoroacetic acid, better kinetics were achieved, however, there was also a substantial decrease in selectivity (Table 1, entries 18–19). The use of a Lewis acid ($AlCl_3$) gave a conversion of over 90%, but a slower reaction (Table 1, entry 20). The bases DBU and CsOAc gave low conversions or only traces of the desired product (Table 1, entries 21–22). From an economic and a selectivity point of view, one equivalent of acetic acid proved to be optimal. Utilizing these optimized conditions, phenyl(pyridin-2-yl)methanone (**2a**) was isolated in 80% yield, starting from **1a** (Table 2, entry 1). When the reaction

[*] J. De Houwer, Prof. Dr. K. Abbaspour Tehrani, Prof. Dr. B. U. W. Maes
Organic Synthesis, Department of Chemistry, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)
E-mail: bert.maes@ua.ac.be

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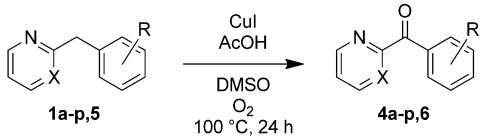
Table 1: Reaction parameter optimization for the oxidation of 2-benzylpyridine (**1a**).

Entry	Cu source	Loading [mol%]	Add.	Equiv add.	Solvent	Conversion[a] [%] (4 h)		(8 h)		(24 h)	
						3a	**4a**	**3a**	**4a**	**3a**	**4a**
1	$Cu(OAc)_2 \cdot H_2O$	15	AcOH	5	DMSO	nd	nd	nd	nd	6	94
2	$Cu(OAc)_2 \cdot H_2O$	5	AcOH	5	DMSO	nd	nd	nd	nd	12	78
3	$Cu(OAc)_2 \cdot H_2O$	10	AcOH	5	DMSO	20	58	21	69	11	89
4	none	0	AcOH	5	DMSO	nd	nd	nd	nd	0	4
5	CuOAc	10	AcOH	5	DMSO	19	53	19	75	nd	nd
6	Cu^0	10	AcOH	5	DMSO	10	42	18	69	9	90
7	$CuBr_2$	10	AcOH	5	DMSO	12	85	12	88	nd	nd
8	CuCl	10	AcOH	5	DMSO	25	65	19	78	nd	nd
9	CuBr	10	AcOH	5	DMSO	23	69	15	83	nd	nd
10	CuI	10	AcOH	5	DMSO	10	88	9	90	nd	nd
11	CuI (99.999%)	10	AcOH	5	DMSO	10	86	8	92	nd	nd
12	CuI	10	AcOH	5	DMA	9	60	7	84	nd	nd
13	CuI	10	AcOH	5	toluene	2	70	0	75	nd	nd
14	CuI	10	AcOH	5	dioxane	4	78	2	88	nd	nd
15	**CuI**	**10**	**AcOH**	**1**	**DMSO**	**3**	**59**	**2**	**81**	**0**	**100**
16	CuI	10	none	0	DMSO	0	3	0	3	0	4
17	CuI	10	PivOH	1	DMSO	5	53	8	79	3	97
18	CuI	10	$PhCO_2H$	1	DMSO	17	76	14	85	8	92
19	CuI	10	TFA	1	DMSO	20	54	22	74	4	96
20	CuI	10	$AlCl_3$	1	DMSO	0	10	5	26	10	82
21	CuI	10	DBU	1	DMSO	0	6	0	10	0	20
22	CuI	10	CsOAc	1	DMSO	0	trace	0	trace	0	trace

[a] Corrected GC-FID conversions of **1a** into **3a** & **4a** after the given time. Reactions were performed on a 0.5 mmol scale at 100°C. nd = not determined.

Table 2: Cu-catalyzed oxidation of substituted 2-benzylpyri(mi)dines.[a]



1a-p,5 → **4a-p,6**

Entry	Substrate	R	X	Product	Yield[b] [%]
1	**1a**	H	H	**4a**	80
2	**1b**	*p*-SCH_3	CH	**4b**	79
3	**1c**	*p*-OCH_3	CH	**4c**	80
4	**1d**	*m*-OCH_3	CH	**4d**	74
5	**1e**	*o*-OCH_3	CH	**4e**	73
6	**1f**	*p*-CH_3	CH	**4f**	69
7	**1g**	*p*-Cl	CH	**4g**	85
8	**1h**	*p*-F	CH	**4h**	85
9	**1i**	*o*-F	CH	**4i**	61
10	**1j**	*p*-COOMe	CH	**4j**	63
11	**1k**	*m*-COOMe	CH	**4k**	67
12	**1l**	*o*-COOMe	CH	**4l**	71
13	**1m**	*p*-CN	CH	**4m**	65
14	**1n**	*m*-CN	CH	**4n**	69
15	**1o**	*p*-CHO	CH	**4o**	61
16	**1p**	*m*-NO_2	CH	**4p**	77
17	**5**	*p*-Cl	N	**6**	67

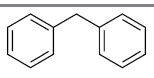
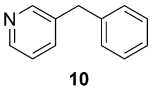
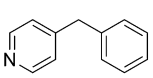
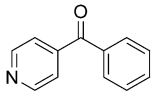
[a] Conditions: substrate (0.5 mmol), AcOH (1 equiv), CuI (10 mol%), DMSO, O_2, 100°C, 24 h. [b] Yield of isolated product.

was repeated on a 5 mmol scale instead of 0.5 mmol, **2a** was isolated in a similar yield (87%), which illustrates the scalability of the oxidation process.

To determine the scope of our oxidation protocol, a variety of substituted 2-benzylpyridines (**1a–p**) that have electron-donating as well as electron-withdrawing groups in the arene were subjected to the optimized oxidation conditions.[8] The corresponding phenyl(pyridin-2-yl)methanones (**4a–p**) were obtained in moderate to good yields (Table 2, entries 2–16), thus, the oxidation method is compatible with a wide range of functional groups. *Para*, *meta* as well as *ortho* substitution of the arene group was tolerated and, in spite of their sensitivity towards oxidation, even a thioether and an aldehyde functionality were left untouched (Table 2, entries 2 and 15). Replacement of the pyridinyl for a diazinyl entity was also attempted. Gratifyingly, when 2-(4-chlorobenzyl)pyrimidine (**5**) was subjected to the optimized oxidation protocol, (4-chlorophenyl)(pyrimidin-2-yl)methanone (**6**) was obtained in 67% yield (Table 2, entry 17).

Next, we investigated the oxidation of different benzylic and picolinic substrates. When diphenylmethane (**7**) was subjected to the optimized reaction conditions, no conversion to either diphenylmethanol (**8**) or benzophenone (**9**) was achieved (Table 3, entry 1). The same result was obtained with 3-benzylpyridine (**10**, Table 3, entry 2), which suggests that the reaction mechanism proceeds by involvement of an imine–enamine tautomerization. This assumption was further supported by the fact that 4-benzylpyridine (**11**) smoothly oxidized under the given reaction conditions, to give phenyl(pyridin-4-yl)methanone (**12**) in 89% yield (Table 3, entry 3). The experiment with **11** also reveals that directed oxidation by precoordination of the metal with the sp^2

Table 3: Cu-catalyzed oxidation of different benzylic substrates.[a]

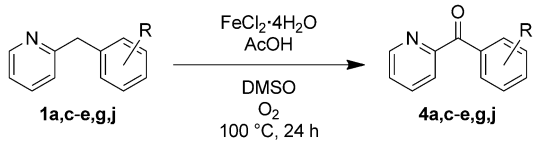
Entry	Substrate	Product	Yield[b] [%]
1	 **7**	none	0
2	 **10**	none	0
3	 **11**	 **12**	89
4	 **13**	none	0

[a] Conditions: substrate (0.5 mmol), AcOH (1 equiv), CuI (10 mol%), DMSO, O_2, 100°C, 24 h. [b] Yield of isolated product.

nitrogen atom is not required. It was also tested whether the oxidation of 2-methylpyridine (**13**) would give the corresponding pyridine-2-carbaldehyde (**14**, Table 3, entry 4). No reaction product was obtained, which suggests that the acidity of the methylene is crucial in this oxidation protocol.

Iron catalysts were also tested in the oxidation reaction.[9] $FeCl_2{\cdot}4H_2O$ proved to be a good catalyst, as full conversion of **1a** was achieved after 24 h at 100 °C to give phenyl(pyridin-2-yl)methanone (**4a**) in 81 % yield (Table 4, entry 1). $FeCl_3{\cdot}6H_2O$ gave similar results, which suggests an initial

Table 4: Fe-catalyzed oxidation of substituted 2-benzylpyridines.[a]



Entry	R	Product	Yield[b] [%]
1	H	**4a**	81
2	*p*-OCH_3	**4c**	81
3	*m*-OCH_3	**4d**	79
4	*o*-OCH_3	**4e**	74
5	*p*-Cl	**4g**	83
6	*p*-COOMe	**4j**	59

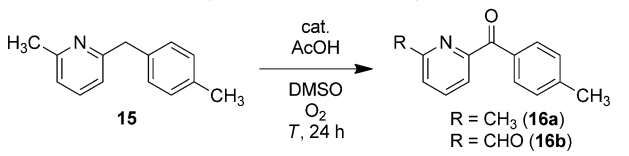
[a] Conditions: substrate (0.5 mmol), AcOH (1 equiv), $FeCl_2{\cdot}4H_2O$ (10 mol%), DMSO, O_2, 100 °C, 24 h. [b] Yield of isolated product.

oxidation when Fe^{II} salts are used. To exclude the possibility that a Cu impurity in the Fe catalyst is performing the actual catalysis, a highly pure source was tested [$FeCl_2$ (99.998 %) and $FeCl_3$ (99.99 %)], which gave only slightly better results.[10]

Other Fe^{III} salts, $Fe(OAc)_3$ and $Fe(acac)_3$, gave only low conversions after 24 h (18 % and 31 % yield, respectively). A set of substrates, which feature both electron-donating and electron-withdrawing substituents, was subjected to these Fe-catalyzed conditions to check for possible differences in the scope of the two metal catalysts. Interestingly, the substituted 2-benzylpyridines (**1a**,**c**–**e**,**g**,**j**) gave similar results to the Cu-based protocol (Table 4, entries 2–6).

To probe the chemoselectivity of our reaction protocols, we investigated the oxidation of 6-(4-methylbenzyl)-2-methylpyridine (**15**), a substrate that contains three chemically different benzylic positions, under Cu or Fe catalysis. With CuI as the catalyst, (4-methylphenyl)(6-methylpyridin-2-yl)methanone (**16a**) was obtained in 41 % yield at 100 °C, together with an 8 % yield of the double oxidation product 6-(4-methylbenzoyl)pyridine-2-carbaldehyde (**16b**) (Table 5, entry 1). Raising the reaction temperature to 130 °C without changing other reaction parameters gave **16b** as the sole reaction product in 62 % yield (Table 5, entry 2). Only traces of oxidation of the carbaldehyde into the corresponding carboxylic acid were detected. When $FeCl_2{\cdot}4H_2O$ was used, only the methylene entity oxidized, both at 100 °C and 130 °C, which gave the mono oxidation product **16a** in 85 % yield (Table 5, entries 3–4). This exemplifies that our protocol allows a chemoselective oxidation. By selecting the proper

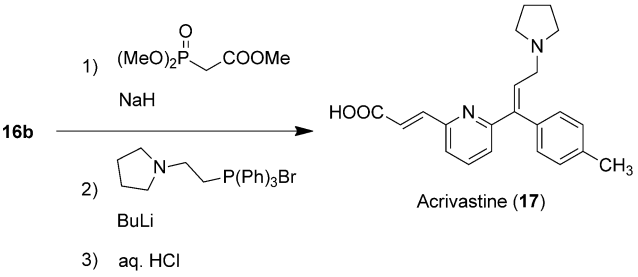
Table 5: Chemoselectivity of Cu- versus Fe-catalyzed oxidation.[a]



Entry	Catalyst	*T* [°C]	Product	Yield[b] [%]
1	CuI	100	**16a**	41
			16b	8
2	CuI	130	**16b**	62
3	$FeCl_2{\cdot}4H_2O$	100	**16a**	85
4	$FeCl_2{\cdot}4H_2O$	130	**16a**	85

[a] Conditions: substrate (0.5 mmol), AcOH (1 equiv), catalyst (10 mol%), DMSO, O_2, *T*, 24 h. [b] Yield of isolated product.

base-metal catalyst, one or two benzylic positions will be oxidized at the same reaction temperature, leaving the third reaction site always intact.[11] 6-(4-Methylbenzoyl)pyridine-2-carbaldehyde (**16b**) is a very interesting compound as it can be further transformed into the antihistamine Acrivastine (**17**) by subsequent Wadsworth–Emmons and Wittig reactions (Scheme 2).[12]



Scheme 2. Synthesis of Acrivastine (**17**) from **16b**.

In summary, we have developed a sustainable oxidation protocol for aryl(di)azinylmethanes that is based on base-metal catalysts (Cu and Fe) and O_2 as the stoichiometric oxidant. These methods possess excellent functional group compatibility and the choice of catalyst can determine the chemoselectivity of the reaction when other benzylic substituents are present. The ketone reaction products are important intermediates for the synthesis of several pharmaceuticals. Further investigations of the scope of the Cu- and Fe-catalyzed oxidation protocol, as well as a study of the reaction mechanism, are currently underway in our laboratory.

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