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Use of Formic Acid as a CO Surrogate for the Reduction of Nitroarenes in the Presence of Dienes: A Two-Step Synthesis of *N*-Arylpyrroles via 1,2-Oxazines

Manar Ahmed Fouad,[a, b] Francesco Ferretti,[a] Simone Galiè,[a] and Fabio Ragaini*[a]

Formic acid, activated by acetic anhydride and a base, was employed as a CO surrogate to deoxygenate nitroarenes to nitrosoarenes, a reaction catalyzed by a palladium/phenanthroline complex in the homogeneous phase. Nitrosoarenes were trapped by conjugated dienes to give 3,6-dihydro-2*H*-[1,2]-oxazines. The latter were then transformed into *N*-arylpyrroles employing CuCl as the catalyst. The reaction was designed to give the best results for pyrroles lacking any substituent in the 2 and 5 positions, which are difficult to produce employing most pyrrole syntheses.

Introduction

1,2-Oxazines are interesting compounds both as bioactive molecules[1] and synthetic intermediates.[1a,b,2] Among them, 1,2-oxazines bearing an aryl ring on the nitrogen atom are typically prepared by the hetero Diels-Alder [4+2] cycloaddition reaction between a nitrosoarene and a dienes.[1b,2a–g,3] However, very few nitrosoarenes are commercially available; they have limited stability and are also well-known cancer promoters. Although it has been reported that the required nitrosoarenes can be generated in situ by oxidation of *N*-arylhydroxylamines[4] or anilines,[5] both approaches have limited synthetic utility. Many years ago, one of us reported that synthetically useful amounts of 3,6-dihydro-2*H*-[1,2]-oxazines could be obtained from nitroarenes and conjugated dienes by employing carbon monoxide as the reductant and either ruthenium[6] or palladium[7] complexes as catalysts, with the palladium-based system performing better both in terms of catalytic efficiency and selectivity. In general, the use of pressurized carbon monoxide to reduce nitroarenes is a very versatile strategy for the synthesis of many different *N*-heterocycles[8] and the only stoichiometric product is CO_2, which is immediately separated from the other products of the reaction when the autoclave is vented. However, few laboratories are equipped to handle pressurized CO, and this severely limits the application of these reactions. The problem is common to other carbonylation reactions and in the last decade several solid or liquid substances have been developed, so-called CO surrogates, which can liberate CO under the reaction conditions either in the same thick-glass reactor where the carbonylation reaction occurs or in a separate reactor connected to the first one (Scheme 1).[9]

In recent years, we have successfully employed phenyl formate as a CO surrogate[10] for the synthesis of indoles from *o*-nitrostyrenes,[11] or from β-nitrostyrenes,[12] for the synthesis of

[a] *M. A. Fouad, Dr. F. Ferretti, S. Galiè, Prof. F. Ragaini*
Department of Chemistry
Università degli Studi di Milano
Via C. Golgi 19
20133 Milano (Italy)
E-mail: fabio.ragaini@unimi.it

[b] *M. A. Fouad*
Chemistry Department
Faculty of Science
Alexandria University
P.O. Box 426
Alexandria 21321 (Egypt)

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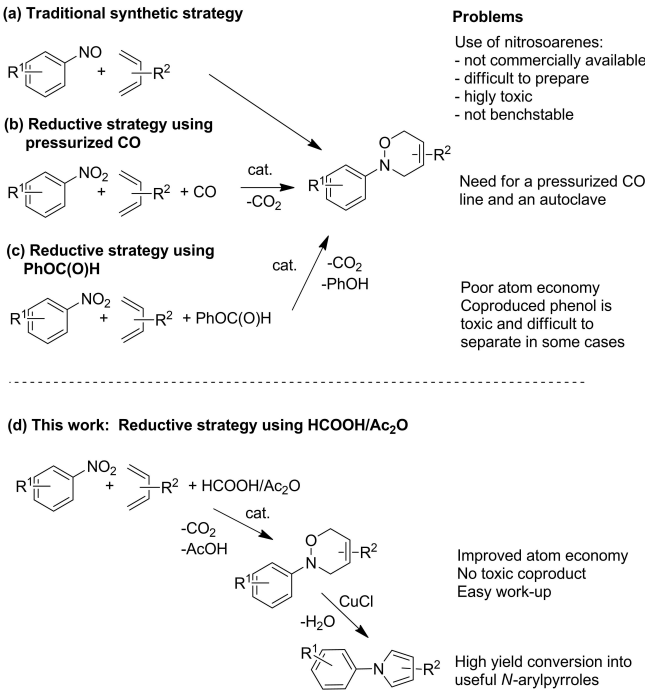

Scheme 1. Known and improved synthetic strategies.

carbazoles from *o*-nitrobiphenyls,[13] and even for the synthesis of oxazines by reaction of nitroarenes with conjugated dienes.[14] Despite these reactions allow obtaining the desired products in high yields, the separation of the phenol produced in the decomposition of phenyl formate can be annoying in some cases. In the literature, $Mo(CO)_6$,[15] $Co_2(CO)_8$,[16] and benzenetriformate[17] have also been employed as CO surrogates in the field of the synthesis of *N*-heterocycles by reduction of nitroarenes, but they also produce stoichiometric byproducts whose separation may complicate the work-up. To solve this problem, we recently developed the use of the formic acid/acetic anhydride mixture[18] to prepare indoles from *o*-nitrostyrenes[19] and 4-quinolones from 2′-nitrochalcones.[20] The use of this mixture, from which the mixed anhydride is generated *in situ*, not only avoids the coproduction of phenol but also saves a synthetic step and improves the atom economy of the full process because phenyl formate is itself prepared by the reaction of phenol with an excess of HCOOH/Ac_2O. Part of the present work is dedicated to the development of suitable experimental conditions to employ the HCOOH/Ac_2O mixture to reduce nitroarenes in the presence of conjugated dienes to give oxazines.

We have previously mentioned that 1,2-oxazines can be further transformed into other interesting compounds. Among these transformations, the dehydration reaction to give pyrroles has a high potential synthetic interest. It should be noted that several synthetic approaches are available for the synthesis of pyrroles, but few of them are applicable to *N*-arylpyrroles.[21] Moreover, most synthetic methods give the best results for pyrroles bearing one or two substituents in the 2 and 5 positions.[22,23] On the contrary, the two-step procedure here reported is best suited for pyrroles that are only substituted in the 3 and 4 positions.

It has long been known that oxazines bearing electronwithdrawing groups on the oxazine ring easily evolve into pyrroles in the presence of bases or acids, but no reaction occurs in the absence of such substituents.[24] Photochemical activation of the oxazine apparently works even in the absence of EW groups,[25] but the best reported yield in pyrrole was 61%. Rhodium[26] and ruthenium[6] complexes have been reported to catalyze the oxazine-pyrrole transformation, but in low yields. We have earlier reported that thermal decomposition of *in situ* generated 3,6-dihydro-2*H*-[1,2]-oxazines at 200 °C results in the formation of *N*-arylpyrroles[7] However, despite the simplicity of the two steps-one pot procedure, only a fair selectivity in the oxazine-pyrrole conversion was achieved. Moreover, a low-boiling point solvent for this reaction would not be compatible with the use of a glass pressure tube and high boiling point solvents may cause severe product losses due to the volatility of several pyrroles. More recently, Sajiki, Sawama, and coworkers reported that an heterogeneous Cu/C catalyst is effective in catalyzing the conversion of 3,6-dihydro-2*H*-[1,2]-oxazines into pyrroles, but despite the high yields obtained in several cases, the only pyrrole lacking any substituent in both the 2 and 5 positions was obtained in only 35% yield.[27] Use of CuCl in methanol afforded pyrroles in a specific system,[28] but only an aminoalcohol was obtained in the absence of specific substituents.[29] Thus, it is clear that a general method for the conversion of 3,6-dihydro-2*H*-[1,2]-oxazines into pyrroles is still lacking.

Results and Discussion

Synthesis of 3,6-dihydro-2H-[1,2]-oxazines

The synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine (**3 aa**) by reaction of nitrobenzene (**1 a**) with 2,3-dimethylbutadiene (**2 a**) was chosen for the optimization of the reaction conditions. The combination of a palladium salt or complex with phenanthroline as a ligand forming the active species *in situ* was chosen because this kind of system has been shown to give very active catalytic systems when CO is used as a reductant/carbonylating agent for nitroarenes and nitroalkenes not only when applied to the synthesis of fine chemicals,[30,31] but even when the more requesting, in terms of activity, synthesis of carbamates or ureas is targeted.[32]

We started our study from the experimental conditions previously optimized for the corresponding reaction employing phenyl formate as the CO surrogate,[14] simply substituting the latter with an equimolar amount of HCOOH (FA) and Ac_2O (Table 1, run 1). However, despite the almost complete conversion observed, the selectivity in oxazine was much lower than that achieved with the use of phenyl formate and increasing the reaction time did not improve the yield because the increase in conversion was accompanied by a decrease in selectivity (run 2). An extensive optimization study was thus performed. The most significant results are reported in Table 1. The full list of experiments is reported in the Supporting Information (Table S1). The main trends that emerge from the analysis of the data are summarized in the following: Use of Na_2PdCl_4 in place of $Pd(MeCN)_2Cl_2$ affords slightly better results, but $Pd(OAc)_2$ gives a less selective reaction. In a previous work on the synthesis of indoles, we had found that the use of a CH_3CN/DMF 9:1 solvent mixture gave quite better results than the use of either solvent alone.[11a] This effect was also found for the present system. A low polarity solvent, toluene, was unsuitable. The use of differently substituted phenanthrolines gave worse results. In general, the selectivity of the reaction decreased as the donating power of the phenanthroline ligand increased in the order 4,7-dichloro-1,10-phenanthroline (Cl_2Phen) < Phen < 4,7-dimethyl-1,10-phenanthroline (Me_2Phen) < 3,4,6,7-tetramethyl-1,10-phenanthroline (TMPhen) - < 4,7-dimethoxy-1,10-phenanthroline ($(MeO)_2$Phen), but the very low conversion obtained with Cl_2Phen makes it unsuitable as a ligand even if it afforded the best selectivity. The best yields were obtained by employing 3 equiv. each of HCOOH, Ac_2O and Et_3N as the base with respect to nitrobenzene. Different reagent ratios or the use of the inorganic bases Na_3PO_4 or Na_2CO_3 were less effective. Oxazine yield increased as the diene/nitrobenzene mole ratio was increased from 2 to 4 and then to 6, but a further increase to 8 gave no further improvement. Both increasing and decreasing the reaction temperature with respect to 140 °C afforded worse results.

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Table 1. Optimization of the reaction conditions for the synthesis of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine.[a]

Run	Cat.	**2a**/**1a**	FA/**1a**	Solv.	Conv. %[b]	Select. %[c]	Yield %[b]
1	A	4	4	MeCN	92	58	53
2[d]	A	4	4	MeCN	100	47	47
3	A	4	3	MeCN	87	59	51
4	B	4	4	MeCN	99	55	54
5	A	4	3	MeCN/DMF	96	64	62
6	A	6	3	MeCN/DMF	97	71	69
7	A	8	3	MeCN/DMF	98	71	70
8[e]	A	6	3	MeCN/DMF	96	72	69
9	C	4	3	MeCN/DMF	94	68	64
10	**C**	**6**	**3**	**MeCN/DMF**	**96**	**80**	**77**
11	C	8	3	MeCN/DMF	97	80	77
12	C	2	3	MeCN/DMF	78	51	39
13	C	6	3	DMF	100	73	73
14[f]	C	6	3	MeCN/DMF	92	57	53
15[g]	C	6	3	MeCN/DMF	94	52	49
16[h]	C	6	3	MeCN/DMF	97	38	37
17[i]	C	6	3	MeCN/DMF	3	82	3
18[j]	C	6	3	MeCN/DMF	16	70	25
19[k]	C	6	3	MeCN/DMF	59	72	42
20	D	6	3	MeCN/DMF	>99	68	68
21[l]	D	4	2.5	Acetone	100	48	48

[a] Experimental conditions: $PhNO_2$ = 0.5 mmol, catalyst 1 mol%, Phen = 2.5 mol%, HCOOH/Ac_2O/Et_3N mol ratio = 1 : 1 : 1, solvent = 10 mL (MeCN/DMF = 9 : 1 where relevant), T = 140 °C, for 4 h. Catalyst: A = $Pd(MeCN)_2Cl_2$, B = $Pd(OAc)_2$, C = Na_2PdCl_4, D = $Pd(acac)_2$. [b] Calculated with respect to the starting $PhNO_2$, measured by GC. [c] Calculated with respect to the reacted $PhNO_2$, measured by GC. [d] Reaction time 8 h. [e] MeCN/DMF = 8 : 2. [f] Me_2Phen was used in place of Phen. [g] TMPhen was used in place of Phen. [h] $(MeO)_2$Phen was used in place of Phen. [i] Cl_2Phen was used in place of Phen. [j] Na_3PO_4 (1 equiv. with respect to **1a**) was employed in place of Et_3N. [k] Na_2CO_3 (1.5 equiv. with respect to **1a**) was employed in place of Et_3N. [l] 110 °C, 10 h.

Finally, we also tested the use of $Pd(acac)_2$ as catalyst because the use of this complex in acetone as the solvent had given the best results when the HCOOH/Ac_2O mixture had been employed for the reductive cyclization of *o*-nitrostyrenes to indoles,[19] but neither when employing the conditions optimized in this work nor when using those optimized for the synthesis of indoles afforded improved yields. In the end, the best yield, 77%, was obtained by working under the conditions of run 10 in Table 1.

Having optimized the reaction conditions, we investigated the reaction scope. Results are shown in Table 2.

First of all, we were glad to find that oxazine **3aa** could be isolated from the reaction mixture with negligible losses (from 77% GC yield, run 10 in Table 1, to 76% isolated, run 1 in Table 2). As far as functional groups are concerned, fluorine, chlorine and bromine substituents were well tolerated, as were the electronwithdrawing groups CN and CF_3. The moderately electrondonating alkyl groups in the *para* position performed well, although in the case of the methyl group the reaction time had to be increased to 16 h to complete the conversion of the nitroarene. However, very low yields were obtained in the case of *p*-methoxynitrobenzene (**1h**). This was not unexpected because this kind of substrate is known to be very problematic for this kind of reaction for two reasons. First, it has been shown in numerous cases that the activation of nitroarenes by low valent transition metal complexes involves an electron transfer from the metal to the nitroarene[33] and this step is retarded by strongly donating substituents on the nitroarene. Second, not only hetero-Diels-Alder reactions are disfavored by electrondonating groups on the dienophile, but **1h** is also in equilibrium with a quinonoid form[34] that cannot be involved in such a reaction. That at least a measurable amount of **3ha** could be obtained under the present conditions represents anyway a positive result because only trace amounts of this oxazine could be detected in previous related works.[7,14] Results were somewhat better when the donating power of the oxygen atom in the para position was attenuated by the presence of an acyl group (**1i**). Steric hindrance in the ortho position was tolerated, but at the expense of a diminished yield. An interesting case is that in which the phenyl ring is substituted by a pyridine one (**3ma**). The corresponding nitropyridine is commercially available as the corresponding *N*-oxide (**1m**). Use of the latter without any pretreatment resulted not only in the reduction of the nitro group to nitroso, but also in the deoxygenation of the *N*-oxide group. Note that this oxazine is very reactive and starts to decompose in the air after a few hours even in the solid state.

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Table 2. Substrate scope for the synthesis of oxazines.[a]

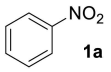
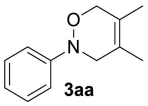
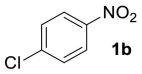
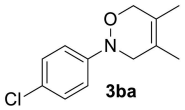
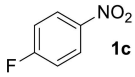
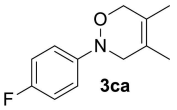
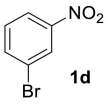
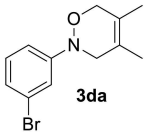
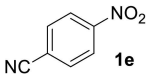
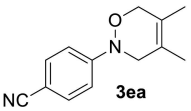
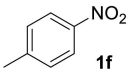
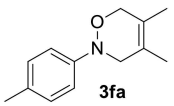
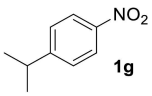
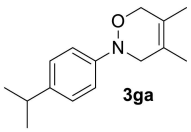
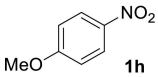
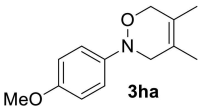
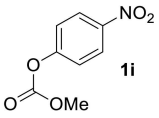
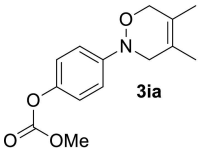
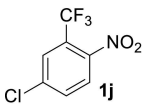
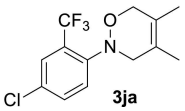
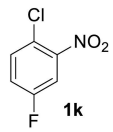
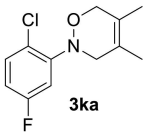
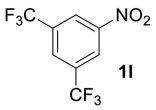
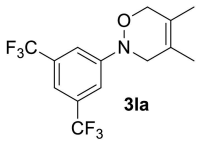
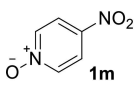
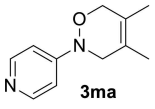
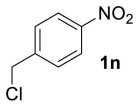
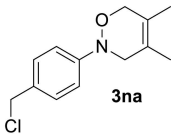
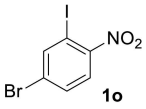
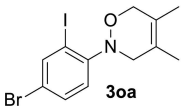
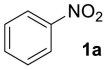
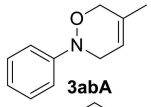
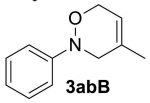
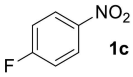
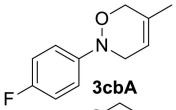
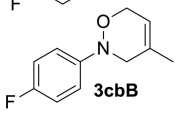
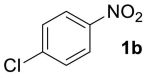
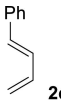
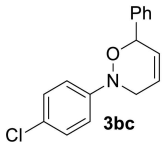
Run	Nitroarene	Diene	Oxazine	Yield %[b]
1	 **1a**	 **2a**	 **3aa**	76
2	 **1b**	 **2a**	 **3ba**	77
3	 **1c**	 **2a**	 **3ca**	58
4	 **1d**	 **2a**	 **3da**	65
5	 **1e**	 **2a**	 **3ea**	43[c]
6	 **1f**	 **2a**	 **3fa**	26 (60)[d]
7	 **1g**	 **2a**	 **3ga**	70
8	 **1h**	 **2a**	 **3ha**	12[c]
9	 **1i**	 **2a**	 **3ia**	22[c]
10	 **1j**	 **2a**	 **3ja**	24
11	 **1k**	 **2a**	 **3ka**	50
12	 **1l**	 **2a**	 **3la**	70
13	 **1m**	 **2a**	 **3ma**	32

Table 2. continued

Run	Nitroarene	Diene	Oxazine	Yield %[b]
14	 **1n**	 **2a**	 **3na**	N.D.
15	 **1o**	 **2a**	 **3oa**	N.D.
16	 **1a**	 **2b**	 **3abA**  **3abB**	50 (A:B = 1:6)
17	 **1c**	 **2b**	 **3cbA**  **3cbB**	57 (A:B = 1:6)
18	 **1b**	 **2c**	 **3bc**	59

[a] Experimental conditions: $PhNO_2$ = 0.5 mmol, Na_2PdCl_4 1 mol%, Phen = 2.5 mol%, HCOOH/Ac_2O/Et_3N/$ArNO_2$/diene mol ratio = 3:3:3:1:6, in 10 mL MeCN/DMF (9:1), T = 140 °C, for 5 h. [b] Isolated yield, unless otherwise noted. N.D. = not detected. [c] Yield determined by NMR, mesitylene as an internal standard. [d] Reaction time 16 h.

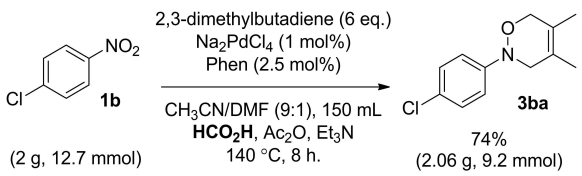
The only nitroarenes for which no oxazine at all could be detected are 4-nitrobenzyl chloride (**1n**) and 2-iodo-4-bromonitrobenzene (**1o**), which contain functional groups that give a fast oxidative addition to low valent metal complexes, likely competitive with the reduction of the nitro group.

When the non-symmetric diene isoprene (**2b**) was employed, a mixture of the two expected regioisomers (distal and proximal) was obtained, with that whose formation is electronically favored in hetero-Diels-Alder reactions prevailing. The two isomers were not separated because they can be converted to the same pyrrole (see next paragraph). The fact that the distal/proximal ratio is similar to that typically observed for the hetero-Diels-Alder reaction of free nitrosoarenes with isoprene suggests that the reaction is occurring off-metal and that free nitrosoarenes are formed. Employing 1-phenyl-1,3-butadiene (**2c**) as the diene, only the proximal isomer was obtained, again in accordance with the literature for the same[5b] or related compounds.[27] It should be noted that nitroarenes and dienes have been recently reported to afford amides when a different catalytic system ($Pd(PPh_3)_4$ with $Mo(CO)_6$ as a CO surrogate) was employed.[35] In this system, the formation of free nitrosoarenes as intermediates was excluded.

Finally, a large-scale (~25 fold) synthesis of **3ba** was performed under the optimized conditions, but with a decreased amount of solvent (15 fold) and a longer reaction time (8 h). The yield was only slightly lower (74% instead of 76%) than that obtained in the smaller scale reaction (Scheme 2).

Dehydration of 3,6-dihydro-2*H*-[1,2]-oxazines to give *N*-arylpyrroles

In search of a general method to transform oxazines into pyrroles, we investigated different reagents and conditions for

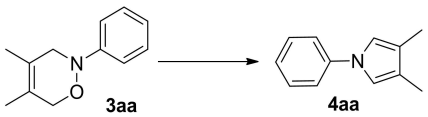


Scheme 2. Large-scale synthesis of **3ba**.

the conversion of **3aa** into 2,3-dimethyl-*N*-phenylpyrrole (**4aa**). The most significant results are reported in Table 3. The full list of experiments is reported in the Supporting Information (Table S2).

We first examined the effect of a high temperature treatment.

Table 3. Optimization of the reaction conditions for the conversion of 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]-oxazine into 3,4-dimethyl-*N*-phenyl-pyrrole.[a]



Run	Cat. [mol%]	Solvent	t [h]	Conv %[b]	Select %[c]	Yield %[b]
1[d]	–	MeCN	3	29	45	13
2[d]	–	Benzene	3	23	55	13
3	–	MeCN	72	13	0	0
4	DBU (25)	MeCN	16	5	79	4
5	NaOH (25)	MeCN	16	26	42	11
6	TfOH (25)	MeOH	16	>99	–	Traces
7	P_2O_5 (25)	MeCN	16	30	28	9
8	Phen (5)	MeCN	48	16	0	0
9	CuCl (20)	MeOH	16	100	44	44
10	CuCl (20)	MeCN	60	96	77	74
11	CuCl (20)	Acetone	5	>99	48	47
12	CuCl (20)	Toluene	15	90	57	51
13	CuCl (20)	MeCN: MeOH[e]	24	84	29	24
14	CuCl (20)	MeCN: H_2O[f]	24	99.7	22	22
15	CuCl/Phen (20/5)	MeCN	16	100	35	35
16	$Cu_2(OH)_3Cl$ (20)	MeCN	72	>99	11	11
17	$Cu_2(OH)_3Cl$/ Phen (20/5)	MeCN	16	>99	35	35
18	$CuCl_2$ (20)	MeCN	3.5	100	5	5
19	$CuCl_2$/Phen (20/5)	MeCN	3.5	100	9	9
20	$CuSO_4 \cdot 5H_2O$ (20)	MeCN	72	96	17	16
21	$CuSO_4 \cdot 5H_2O$/ Phen (20/5)	MeCN	72	100	18	18
22 A	CuCl (10)	MeCN	30	69	50	34
22B	CuCl (+10)[g]	MeCN	60	94	50	47
23	**CuCl (30)**	**MeCN**	**60**	**100**	**77**	**77**

[a] Experimental conditions: 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-[1,2]–oxazine (**3aa**) = 0.25 mmol, at 140 °C, in 2 mL of solvent. [b] Calculated with respect to the starting nitrobenzene, measured by GC. [c] Calculated with respect to the reacted nitrobenzene, measured by GC. [d] The reaction was performed at 200 °C in an autoclave under 20 bars of CO to avoid the boiling of the solvent. [e] MeCN/MeOH = 1:1. [e] MeCN/H_2O = 4:1. [g] 10 mol% CuCl was added to the reaction mixture of run 22 A after 30 h.

However, in the absence of any other substance, the conversion to pyrrole proceeded only with a fair selectivity at 200 °C and no pyrrole was detectable by working at 140 °C. Bases, acids or even an acidic dehydrating agent, P_2O_5, showed some accelerating effect, but failed to give good yields of pyrroles. The use of triflic acid,[36] in particular, gave a complete conversion of the oxazine, but a mixture of products and no pyrrole were obtained.

Since CuCl in methanol had been reported to be effective in promoting the desired transformation in one case,[28] we tested the effect of its addition on our substrate. The conversion was indeed complete, but only a fair 44% yield of pyrrole was obtained. Decreasing the temperature even decreased the selectivity of the reaction to 18%. An investigation of a range of solvents or solvents mixtures showed that acetonitrile was the one affording the best yield, despite the fact that the reaction is quite slow.

Lowering the temperature led to a decreased conversion, with little effect on the selectivity, so 140 °C was chosen as the temperature for further studies, even taking into account that this is the temperature at which the first stage of the reaction was performed. The addition of phenanthroline helped in solubilizing CuCl and accelerated the reaction, but at the expense of selectivity.

Since copper(I) compounds can be easily contaminated by copper(II) compounds if not kept rigorously under an inert atmosphere, we also tested the effect of several copper(II) salts, both in the presence and absence of phenanthroline. At least chlorine-containing copper(II) salts were indeed very active in decomposing the oxazine, but gave very poor yields of pyrrole. Thus, it is clear that any copper(II) contaminating the employed CuCl may cause the formation of byproducts but is not responsible for the formation of most of the pyrrole.

Adding the CuCl in two portions over the time led to worse results, indicating that the long reaction times are not due to a deactivation of the catalyst, but increasing its amount to 30 mol% afforded a satisfying 77% yield (run 23) and we considered this sufficient to proceed with investigating the substrate scope under these conditions. Unfortunately, simply adding 30 mol% CuCl to the reaction mixture after the oxazine synthesis (performed under the optimized conditions, run 10 in Table 1) and performing the conversion to pyrrole under the optimized conditions (run 23 in Table 2) even for a prolonged time (120 h), did not give good results. Only 42% of the oxazine reacted and the pyrrole was obtained with poor selectivity in just 10% yield (run 36, Table S2). Clearly, some of the components of the first catalytic system interfere with the second transformation. Thus, isolating the oxazine before converting it into pyrrole is necessary under the conditions developed in this work.

Having identified the best experimental conditions, the oxazines isolated in the first part of this work, except for those that had been isolated in a too low yield, were converted into pyrroles. Results are shown in Table 4.

The reaction tolerates halogen and alkyl substituents on the aryl ring and affords good yields even when employing a 1-phenyl-1,4-butadiende-derived oxazine **3bd** as the substrate. Unfortunately, poor results were obtained when trifluoromethyl

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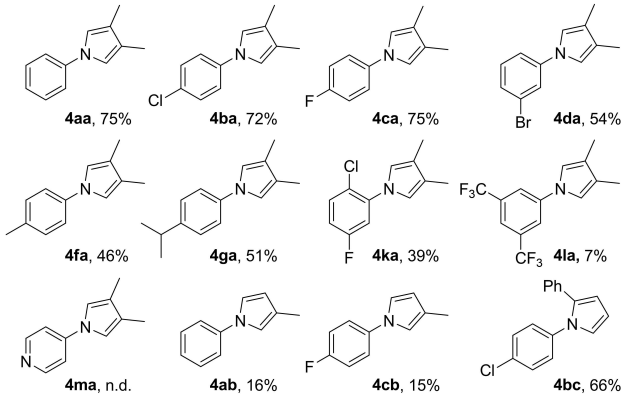
Table 4. Substrate scope for the conversion of oxazines into pyrroles.[a]



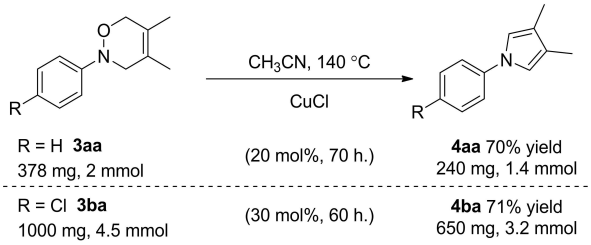
[a] Experimental conditions: 3,6-dihydro-2*H*-[1,2]-oxazine derivative (0.25 mmol), CuCl (0.08 mmol), in CH_3CN (2 mL) at 140 °C for 60 h. Isolated yields are shown.

groups were present or when isoprene-derived oxazines were employed as substrates. In the first case, an immediate blue color developed upon mixing **3la** with CuCl at room temperature, indicating a different and specific reactivity. The low isolated yield of **4ab** and **4cb** is at least in part due to their high tendency to sublime and be evaporated with the solvent. In general, it should be stressed that we encountered this problem even with the other pyrroles, but the problem was more serious for these two products.

Although the yields obtained in several cases may appear to be only fair, it should be stressed that, to the best of our knowledge, apart from **4aa** (that had been previously isolated in a lower yield) and **4ab** (for which many synthetic strategies have been reported), most of the other pyrroles in Table 2 have never been fully characterized previously, indicating that, despite the simplicity of their structure, they are not easily prepared even by other means.

As an exception, a complete lack of reactivity was detected employing a pyridine containing oxazine as the substrate **3ma** which was recovered unconverted (90%) after the reaction. Coordination of the pyridine N-atom to copper is most likely deactivating the catalyst and preventing the oxazine conversion.

Finally, the synthesis of **4aa** and that of **4ba** were also tested on a larger scale (Scheme 3) and even in these cases the product could be isolated with only a small decrease in the yield with respect to the reaction run at the standard concentrations.

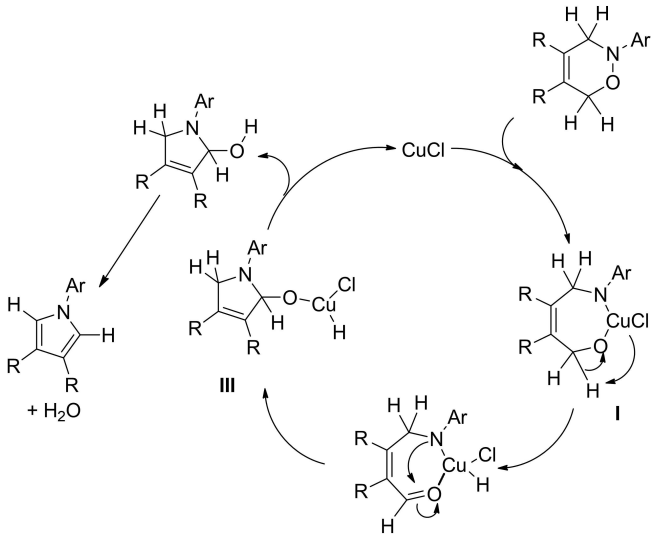


Scheme 3. Scaled-up synthesis of pyrroles **4aa** and **4ba**.

A tentative reaction mechanism for the oxazine ring contraction to pyrroles is shown in Scheme 4. Oxidative addition of the N–O bond to copper chloride is proposed to form intermediate **I**. Although formation of Cu(III) species as intermediates in catalytic cycles is still debated,[37] they have been invoked in several N–O bond cleavage reactions.[38] β-Hydride elimination on the oxygen side of the formed metallacycle **I** leads to the formation of **II**, which in turn goes through an intramolecular ring closure to give the cyclic hemiaminal **III**. Reductive elimination from the copper center and subsequent dehydration/isomerization process lead to pyrrole formation.

Conclusions

In this paper, we tackled two problems. The first is the identification of a cheap, easily operated synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines. In the literature, this type of compounds is often obtained by the reaction of conjugated dienes with nitrosoarenes. However, the preparation of the latter, either as isolated molecules or as labile intermediates, is generally performed under oxidative conditions, which do not allow a broad tolerance of different functional groups. Carbon monoxide, when in the presence of suitable transition metal catalysts, is extremely selective in reducing nitro- to nitrosoarenes without affecting other reducible groups and the procedure can be applied to the synthesis of oxazines, but the use of pressurized CO is not possible in most laboratories. The use of phenyl formate as a CO surrogate represents a solution, but the coproduced phenol can be difficult to separate in some cases. The use of the formic acid/acetic anhydride mixture, investigated in the present work, solves even the last problem, although yields were in several cases higher when phenyl formate was employed. It also represents a better solution even from the atom economy point of view because phenyl formate is itself obtained from phenol and the $HCOOH/Ac_2O$ mixture



Scheme 4. Proposed mechanism for the CuCl mediated conversion of 1,2-oxazines to pyrroles.

and the latter has to be employed in large excess to obtain the formate in a yield that anyway does not go over 80%.

The second problem is the conversion of the obtained oxazines into *N*-arylpyrroles. Even if scattered examples of this transformation have been known for decades, a careful screening of the literature reveals that good yields have only been reported in specific cases, such as the presence of electronwithdrawing substituents on the oxazine ring or of an aryl group in position 2 of the finally obtained pyrrole. An efficient general procedure able to afford pyrroles lacking substituents in both the 2 and the 5 positions by this synthetic strategy was lacking. We found that cuprous chloride can play this role and optimized the reaction conditions to make its employment a synthetically useful tool.

The two reactions together represent an easy entry into *N*-arylpyrroles lacking substituents in both the 2 and 5 positions, a class of interesting molecules difficult to access by other techniques.

Experimental Section

General procedure for the synthesis of 3,6-dihydro-2*H*-[1,2]-oxazines: In order to avoid weighing errors, stock solutions of Na_2PdCl_4 and Phen were prepared by dissolving respectively 29.4 mg of Na_2PdCl_4 in 20 mL dry DMF (to produce a 1.47 mg/mL solution) and 45 mg Phen in 20 mL dry CH_3CN (to produce a 2.25 mg/mL solution) under a dinitrogen atmosphere. In a typical catalytic reaction, the nitrobenzene derivative (0.5 mmol) was weighed in the air and placed in a 23 mL thick-walled glass pressure tube with screw thread (Duran) containing a magnetic stirring bar. The tube was placed inside a Schlenk tube with a wide mouth, evacuated, and filled three times with dinitrogen. 1 mL of each stock solution of the catalysts and Phen was added, and the mixture was stirred for 15 min. to allow the formation of the Pd/Phen complex. Subsequently, diene (3 mmol), triethylamine (1.5 mmol) and acetic anhydride (1.5 mmol) were added without stirring, and then CH_3CN (8 mL) was layered slowly. Finally, formic acid (1.5 mmol) was added, and the pressure tube was sealed under dinitrogen. The order of addition of the reagents and solvent layering is critical to avoid loss of CO which begins to evolve, even at room temperature, as soon as HCOOH, Ac_2O, and the base are mixed. The pressure tube was then placed and heated while stirring in a custom-made aluminum block preheated to 140 °C. At the end of the reaction, the pressure tube was removed from the aluminum block, allowed to cool to room temperature, and slowly opened under a fume hood. After the evaporation of CH_3CN, 10 mL of ethyl acetate were added. The reaction mixture was washed with $NaHCO_3$ (1×10 mL) and water (1×10 mL) in order to get rid of the acetic acid formed during the reaction. The organic layer was collected, dried over Na_2SO_4, filtered and evaporated to get the crude, which was subjected to silica-gel column chromatography using hexane/ ethyl acetate as the eluent with the addition of 1% of Et_3N to partly deactivate acidic sites in the silica gel.

General procedure for the synthesis of *N*-arylpyrroles: 3,6-Dihydro-2*H*-[1,2]-oxazine derivative (0.25 mmol) and CuCl (0.08 mmol) were placed in a pressure tube of the same type used in the previous procedure. The tube was inserted into a wide-mouthed Schlenk tube, evacuated, and then filled three times with dinitrogen. 2 mL of dry CH_3CN were added, and the tube was sealed under dinitrogen and heated at 140 °C for 60 h. After reaction completion, the reaction was allowed to cool to room temperature and slowly opened inside a wide-mouthed Schlenk tube under dinitrogen. CH_3CN was evaporated, and the crude was subjected to silica-gel column chromatography using hexane as the eluent (the eluent was pushed using dinitrogen, and the fractions were collected under dinitrogen) to give the corresponding *N*-arylpyrrole.

Supporting Information

Complete data for the optimization of the reaction conditions for oxazines and pyrrole synthesis, general information, procedure for large-scale syntheses, characterization data for oxazines and pyrroles, copies of NMR spectra. The authors have cited additional references within the Supporting Information.[39]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: homogeneous catalysis · formic acid · nitroarenes · nitrogen heterocycles · CO surrogates

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