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Transition-Metal-Free Intramolecular *N*-Arylations

Isabelle Thomé and Carsten Bolm*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg1, D-52074 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

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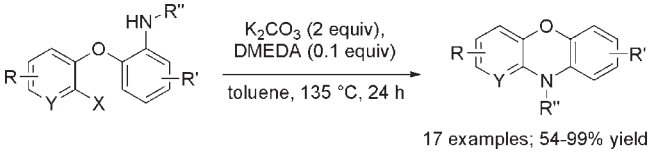
ABSTRACT



17 examples; 54-99% yield

***N*-Substituted phenoxazines and related aza analogs have been prepared from *N*-acetylated aryloxy anilides by transition-metal-free, base-catalyzed cyclization reactions. In the presence of a mixture of 10 mol % of *N,N'*-dimethylethylenediamine (DMEDA) and 2 equiv of K_2CO_3 in toluene at 135 °C the products are obtained in high yields.**

Transition-metal-catalyzed cross-coupling reactions to form carbon−heteroatom bonds constitute a powerful tool in pharmaceutical and medicinal chemistry.[1] In the past, numerous protocols for inter- and intramolecular C−N, C−O, and C−S bond formations have been developed, and most of them involve the catalytic use of Pd complexes or Cu salts. Despite remarkable advances the oftentimes needed high catalyst loadings in combination with sophisticated ligands as well as the strict demand for the absence of any transition metal impurity in the final product can render such processes cost-intensive and affect their practicability. Thus, the development for alternative approaches toward "cross-coupling products" is highly desirable, and in this context, transition-metal-free protocols appear particularly attractive. Recently, various groups reported significant progress in this area including transition-metal-free C−H arylations to construct biphenyl frameworks.[2,3] Our own work has been focused on the use of the simple mixture of KOH and DMSO as a *superbasic medium*[4] for the transition-metal-free preparation of cross-coupling products.[5] Here, we describe DMEDA-catalyzed intramolecular C−N bond formations with K_2CO_3 as a base leading to a wide range of acetylated phenoxazine derivatives and aza analogs thereof.[6]

Phenoxazines are tricyclic heterocycles which have found use as therapeutic agents and scaffolds in medicinal chemistry.[7] Due to their photophysical properties[8]

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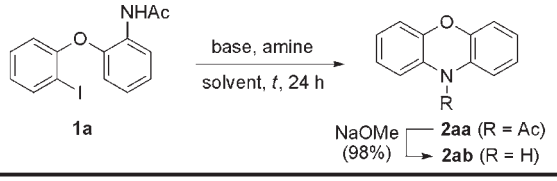
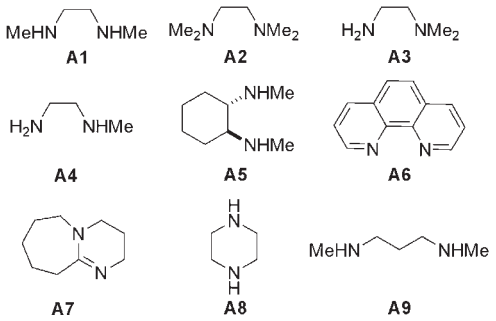
Table 1. Optimization of the Intramolecular C−N Bond Formation[a]



entry	base	amine	solvent	t °C	yield of **2aa** %[b]
1	K_2CO_3	A1	toluene	135	91
2	K_2CO_3	none	toluene	135	-
3	none	A1	toluene	135	-
4	Cs_2CO_3	A1	toluene	135	47
5	$K_3PO_4•H_2O$	A1	toluene	135	traces
6	NaOEt	A1	toluene	135	traces[c]
7	KO*t*-Bu	A1	toluene	135	traces[d]
8	NaO*t*-Bu	A1	toluene	135	traces[d]
9	K_2CO_3[e]	A1	toluene	135	90
10	K_2CO_3[f]	A1	toluene	135	57 (23)
11	K_2CO_3	A1	toluene	120	20
12	K_2CO_3	A1	toluene	100	traces
13	K_2CO_3	A1	DMSO	135	traces
14	K_2CO_3	A1	DMF	135	traces
15	K_2CO_3	A1	dioxane	135	76
16	K_2CO_3	A2	toluene	135	traces
17	K_2CO_3	A3	toluene	135	-
18	K_2CO_3	A4	toluene	135	-
19	K_2CO_3	A5	toluene	135	90
20	K_2CO_3	A6	toluene	135	-
21	K_2CO_3	A7	toluene	135	72
22	K_2CO_3	A8	toluene	135	traces
23	K_2CO_3	A9	toluene	135	9



[a] Reaction conditions: **1a** (0.28 mmol), base (2.0 equiv), amine (0.1 equiv), toluene (1 mL), 24 h, 135 °C. [b] After column chromatography. [c] Formation of 58% (GC) of NH-phenoxazine **2ab**. [d] Formation of 98% (GC) of NH-phenoxazine **2ab**. [e] Use of K_2CO_3 with a purity of >99.999%. [f] Use of less base (1.5 and 1.0 equiv, respectively).

phenoxazines have been applied as dyes in dye-sensitized solar cells[9] and chemosensors.[10] Common preparations of phenoxazines involve Smiles rearrangements of 2′-aminodiaryl ethers[11] or reactions between *o*-aminophenols and chalcones.[12] An alternative protocol giving access to less substituted derivatives relies on Cu catalysis.[13] Our goal was to find a *transition-metal-free N*-arylation protocol providing phenoxazines under base catalysis starting from adequately *N*-protected aniline derivatives.

For the initial phase of our research, *N*-[2-(2-iodophenoxy)-phenyl]acetamide (**1a**) was selected as starting material. For two reasons, this compound appeared particularly suitable: First, it could be prepared through a transition-metal-free three-step reaction sequence starting from 2-iodophenol,[14] which allowed us to minimize the presence of trace metal impurities in the starting materials thereby reducing the potential of a catalytic impact of such metal species.[15,16] Second, the acetyl group of product **2aa** could be cleaved with NaOMe[17] providing 10*H*-phenoxazine **2ab** in excellent yield (98%). This transformation expanded the synthetic potential of the heterocyclic core for subsequent applications. The results of the optimization study for the conversion of **1a** into phenoxazine **2aa** are presented in Table 1.

Various combinations of bases, amines, solvents, and temperatures were screened. Finally, the best result was obtained when **1a** was treated with a catalytic amount of DMEDA (10 mol %) and K_2CO_3 (2 equiv) in toluene at 135 °C for 24 h. Under those conditions, phenoxazine **2aa** was formed in 91% yield (Table 1, entry 1).

Control experiments confirmed that in the absence of either DMEDA or K_2CO_3 no product was formed (entries 2 and 3). Bases other than K_2CO_3 proved less efficient or were not suitable at all. Thus, with Cs_2CO_3 instead of K_2CO_3 phenoxazine **2aa** was isolated in 47% yield (entry 4), and only traces of the product were detected when $K_3PO_4·H_2O$, NaOEt, KO*t*-Bu, or NaO*t*-Bu were used (entries 5−8). With the latter three bases significant

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(16) Great care was taken to avoid the presence of transition metal impurities. All starting materials were synthesized without using any transition metal (e.g., reduction of the nitro-group with $SnCl_2·2H_2O$ instead of Fe/acetic acid). Reagent transfers were performed with one-way plastic spatulas, and new glassware and unused stirring bars were used for the cyclization reactions. The starting materials and reagents were analyzed to the detection limit of 4 ppb by atomic absorption spectroscopy (AAS) or inductively coupled mass spectroscopy (ICP-Ms). The following data were obtained: (**1a**) Cu <4 ppb, Pd <4 ppb; (K_2CO_3) Cu <4 ppb, Pd <4 ppb; (DMEDA) Cu 2.4 ppm, Pd <4 ppb.

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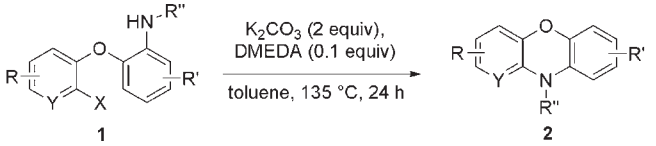
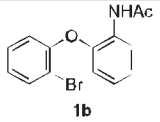
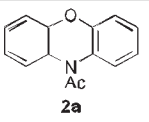
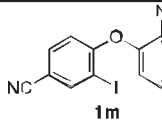
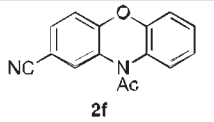
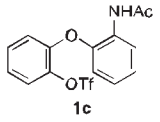
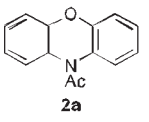
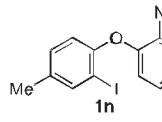
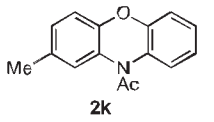
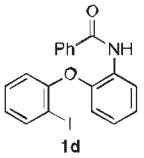
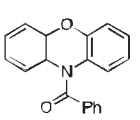
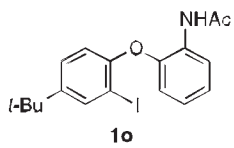
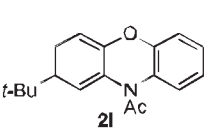
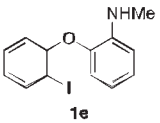
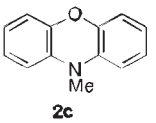
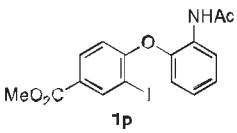
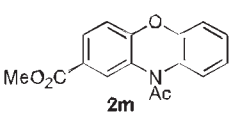
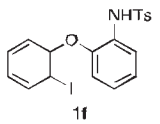
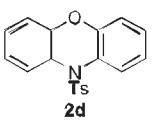
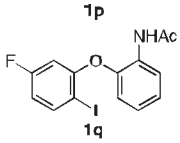
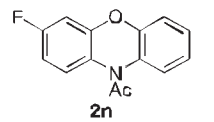
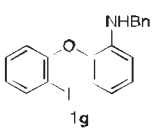
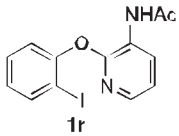
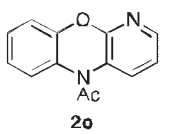
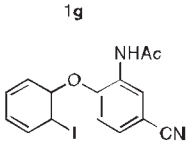
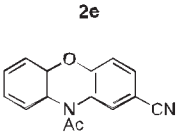
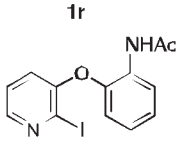
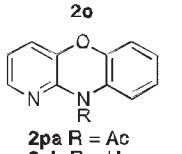
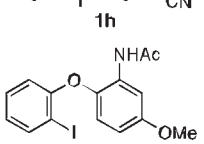
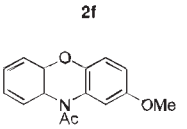
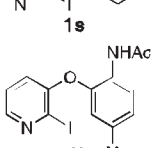
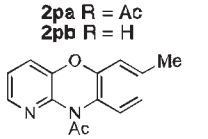
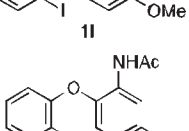
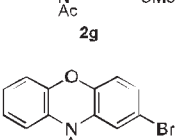
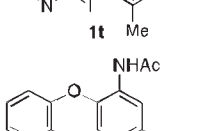
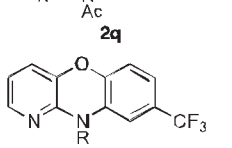
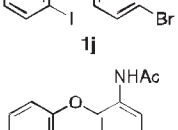
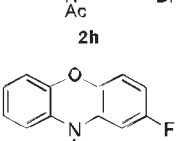
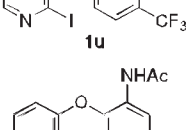
Table 2. Scope of the Intramolecular *N*-Arylation for the Synthesis of Phenoxazines and Derivatives[a]



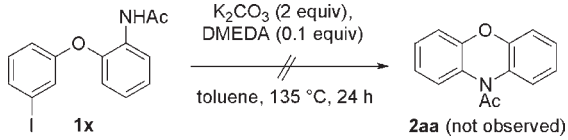
entry	substrate	product	yield %[b]	entry	substrate	product	yield %[b]
1	 **1b**	 **2a**	-	12	 **1m**	 **2f**	54
2	 **1c**	 **2a**	-	13	 **1n**	 **2k**	80
3	 **1d**	 **2b**	38	14	 **1o**	 **2l**	75
4	 **1e**	 **2c**	-	15	 **1p**	 **2m**	69
5	 **1f**	 **2d**	-	16	 **1q**	 **2n**	97
6	 **1g**	 **2e**	-	17	 **1r**	 **2o**	trace
7	 **1h**	 **2f**	64	18	 **1s**	 **2pa** R = Ac **2pb** R = H	100[c]
8	 **1l**	 **2g**	79	19	 **1t**	 **2q**	83
9	 **1j**	 **2h**	86	20	 **1u**	 **2ra** R = Ac **2rb** R = H	100[d]
10	 **1k**	 **2l**	84	21	 **1v**	**2s**	99
11	**1l**	**2j**	84	22	**1w**	**2t**	98

[a] Reaction conditions: substrate (100 mg), base (2.0 equiv), amine (0.1 equiv), toluene (1 mL), 24 h, 135 °C. [b] After column chromatography. [c] Quantitative yield of cyclization products: 20% of **2pa** and 80% of **2pb**. [d] Quantitative yield of cyclization products: 9% of **2ra** and 91% of **2rb**.

amounts (up to 98%) of NH-phenoxazine **2ab** were found.[18]

Considering the importance of trace metals in catalytic reactions,[15] and taking into account that copper had been

Scheme 1. Attempted Cyclization of **1x** To Give **2aa**



applied as a catalyst in related cyclizations,[11c] high-purity K_2CO_3 (> 99.999%) was applied. The yield of **2aa** remained essentially unchanged (90%, entry 9) indicating that remaining metals were not critical.[19] Using less base (than the common 2 equiv) affected the yield of **2aa** negatively (entry 10). Also lowering the reaction temperature from 135 to 120 °C or even 100 °C reduced the yield of **2aa** (entries 11 and 12). DMSO and DMF were unsuitable solvents, and in dioxane instead of toluene the yield of **2aa** was lower (entries 13−15).

Hypothesizing that the diamine (DMEDA) played a major role in the catalysis, other nitrogen-containing compounds were tested. Interestingly, high yields of **2aa** were only obtained in cyclizations with DMEDA (**A1**), *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (**A5**), and DBU (**A7**) with the latter providing product in a lower yield compared to the former two (entries 1, 19, and 21). All other dinitrogen derivatives (**A2**−**A4**, **A6**, **A8**, and **A9**) were much less effective (entries 16−18, 20, 22, and 23). The presence of monoamines Et_3N and $(i\text{-Pr})_2NEt$ did not result in any reaction (data not shown).

Apparently, the combination of K_2CO_3 and DMEDA (in quantities of 2.0 and 0.1 equiv, respectively) was the key component of the catalysis, and it had to be applied in toluene at 135 °C. Subsequently, various substrates were submitted to this catalytic system (Table 2). Attempts to cyclize the corresponding bromo and triflyl derivatives **1b** and **1c**, respectivily, failed revealing that the iodo substituent was essential for the success of the cyclization (entries 1 and 2). Changing the N-substituent from acetyl to benzoyl, methyl, tosyl, or benzyl yielded starting materials (**1d**−**g**) of lower or no reactivity (entries 3−6).[20]

Various other aryloxy acetanilides underwent smooth intramolecular *N*-arylations affording the corresponding phenoxazines (or aza derivatives thereof) in good to excellent yields (entries 7−22). The nature of the substituent linked to the anilide part had almost no effect on the course of the reaction. In this series (entries 7−11), halo-substituted educts gave the highest yields. Varying the substitution pattern of the iodo aryl part showed that the presence of an electron-donating group positively affected the yield of the corresponding phenoxazine, albeit the effect was only minor. In all cases (entries 12−16) good to high yields were achieved.[21]

Whereas aryloxy amido pyridine **1r** gave only a trace of the corresponding cyclized product 5-acetyl-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine (**2o**) (entry 17), acetanilides with 2-iodo pyridinyloxy groups (**1s**−**w**) were highly reactive leading to excellent yields of the corresponding 10*H*-benzo[*b*]pyrido[2,3-*e*][1,4]oxazine derivatives (entries 18−22). In two reactions, even quantitative yields were observed, albeit in both cases mixtures of *N*-acetylated (**2pa** and **2ra**) and deprotected (**2pb** and **2rb**) products were formed.

Preliminary mechanistic investigations and related observations led to the following conclusions: (1) A Smiles rearrangement[10] can be ruled out, because iodo aryloxy acetanilide **1a** did not cyclize in the absence of diamine (DMEDA). (2) Neither cyclization to phenoxazine **2aa** nor dehalogenation was observed in the attempt to react *N*-[2-(3-iodophenoxy)phenyl]acetamide (**1x**) under the standard conditions (Scheme 1). If carbanionic or aryne-type intermediates were involved, those reactions would have been expected in conversions of this starting material (which is isomeric to acetanilide **1a** with respect to the iodo substituent). (3) The addition of TEMPO or 1,1-diphenylethylene as radical scavengers (in equimolar quantities) to a catalyzed transformation of **1a** did not inhibit the cyclization.[2b] In the first case the yield of **2aa** was not affected at all; in the second, it was lowered to 45%. These results suggest that radical species do not play a major role, if any. Further studies are currently ongoing with the goal to reach a better understanding of the underlying reaction principles.

In summary, we have developed a practical synthesis of substituted phenoxazines and aza derivatives thereof. The cyclization step involves the use of a catalytic amount of DMEDA and K_2CO_3 as base. These findings have already proven useful for other investigations on transition-metal-free heteroatom arylation reactions, which are currently ongoing in our laboratories.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Attempts to isolate 10*H*-phenoxazine **2ab** failed. Presumably, decomposition occurred under these conditions due to the light sensitivity of this product.

(19) With 5 mol % catalyst loading the potential of CuI and $CuCl_2$ (both with purities of > 99.999%) in combination with 10 mol% of DMEDA and 2 equiv of K_2CO_3 in toluene at 100 °C to affect formation of **2aa** was confirmed. The yields (39% and 19%, respectively) were significantly higher than the one (traces of product) observed in a reaction performed in the absence of copper under the same reaction conditions.

(20) Also the cyclization of deacetylated **1a** to directly afford **2ab** remained unsuccessful under standard cyclization conditions (with DMEDA and K_2CO_3). After 24 h the starting material was recovered quantitatively.

(21) Also, *N*-{2-[(2-iodophenyl)(methyl)amino]phenyl}acetamide (**1y**) was applied under these conditions, and the corresponding product **2u** was obtained in 40% yield.

The authors declare no competing financial interest.