Cyclizing Radical Carboiodination, Carbotelluration, and Carboaminoxylation of Aryl Amines**

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Abstract: Radical carboiodination of various aryl amines is reported. Aryl diazonium salts, generated in situ from the corresponding aryl amines, are reacted with Bu_4NI to provide the corresponding aryl radicals which undergo 5-exo or 6-exo cyclization. Iodine abstraction eventually affords the carboiodinated products in good to excellent yields. If TEMPO is added, the cascade provides the cyclized carboaminoxylation products. Running the reaction in the presence of PhTeTePh affords the phenyltellurated cyclized products.

Palladium-mediated radical carboiodinations of alkenes using activated alkyl iodides are known.^[1a] Recently this chemistry was extended to aryl iodides by Lautens and Tong.^[1b-e] They showed that appropriately substituted aryl iodides can be isomerized in good yields to the corresponding cyclic alkyl iodides (Scheme 1). Experimental and theoretical



Scheme 1. Carboiodinations.

studies revealed that these cyclizations occur through the migrative insertion of the corresponding aryl–Pd intermediates.^[2] Stimulated by these studies we embarked a program on cyclizing radical carboiodinations using aryl amines as starting materials. One advantage over the existing methods is that with the radical approach it should be possible to conduct the carboiodination under transition-metal-free conditions. Moreover, a quaternary C center next to the C–I bond in the product iodide is not necessary since in the radical pathway β -H elimination, which is a problem in the Pd-mediated process, will not occur.

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We decided to start with aryl amines, which are transformed in situ to the corresponding aryl diazonium salts, as efficient C radical precursors.^[3] Aryl diazonium salts have been successfully used in radical cyclization reactions induced by single-electron-transfer (SET) reagents^[4] and also sodium iodide mediated reactions to give the corresponding iododediazonation products have been reported.^[5] However, not every aryl amine can be readily transformed to the corresponding aryl diazonium salt due to its limited stability and due to problems occurring during isolation. Moreover, some aryl diazonium salts are explosive and care has to be taken during isolation and storage. Therefore, generating aryl diazonium salts in situ under conditions where they can undergo further reaction directly might solve these problems.

In fact, aryl amines have been elegantly used by Wang and co-workers in radical arylations in the in situ generation of the corresponding aryl diazonium salts.^[6] It is important to note that carboiodination cannot be achieved by radical iodine transfer chemistry starting with aryl iodides. This is because the C–I bond in aryl iodides is stronger than that in alkyl iodides and because the aryl radicals are high in energy. Therefore, an alkyl radical cannot abstract an iodine atom from an aryl iodide.^[7] Herein we report useful radical carboiodinations of various aryl amines and will further show that the concept can be also applied to carbotellurations and carboaminoxylations.

Optimization studies were conducted using aryl amine **1a** to provide cyclized alkyl iodide **2a** (Table 1). Reactions were run in acetonitrile and isoamyl nitrite (1.5 equiv) served as the

Table 1: Reaction optimization.

NH ₂ 0 1a	l⁻ source, RONC acid, MeCN RT, 1 h	$2 \rightarrow 2a$	-1
I ⁻ source (equiv)	R (equiv)	Acid (equiv)	Yield [%]
Nal (1.5)	isoamyl (1.5)	MeSO ₃ H (1.1)	68
KI (1.5)	isoamyl (1.5)	MeSO ₃ H (1.1)	77
Csl (1.5)	isoamyl (1.5)	MeSO ₃ H (1.1)	94
Bu₄NI (1.5)	isoamyl (1.5)	MeSO₃H (1.1)	99
Bu₄NI (1.1)	isoamyl (1.5)	MeSO ₃ H (1.1)	68
Bu₄NI (1.5)	isoamyl (1.1)	MeSO ₃ H (1.1)	88
Bu₄NI (1.5)	tert-butyl (1.5)	MeSO ₃ H (1.1)	34 ^[a]
Bu₄NI (1.5)	isoamyl (1.5)	MeSO ₃ H (0.1)	< 5
Bu₄NI (1.5)	isoamyl (1.5)	MeSO₃H (0.3)	5
Bu₄NI (1.5)	isoamyl (1.5)	<i>p</i> -TosOH (1.1)	92
Bu₄NI (1.5)	isoamyl (1.5)	$CF_{3}CO_{2}H$ (1.1)	78
	NH ₂ 1a I [−] source (equiv) Nal (1.5) KI (1.5) CsI (1.5) Bu ₄ NI (1.5)	NH2 I source, RONC acid, MeCN acid, MeCN 1a r source, RONC I ⁻ source (equiv) R (equiv) Nal (1.5) isoamyl (1.5) KI (1.5) isoamyl (1.5) CsI (1.5) isoamyl (1.5) Bu4NI (1.5) isoamyl (1.5)	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

[a] A complex reaction mixture was obtained containing 34% of **2a** as determined by NMR analysis.

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reagent for diazonium salt generation. We chose methanesulfonic acid to induce the formation of the diazonium salt from **1a**. The I salt was slowly added as a MeCN solution over 1 hour. In cases where the salt was not perfectly soluble in MeCN a small amount of water was added.

The initial experiment was conducted with NaI as the formal SET and radical-trapping reagent. We were very pleased to find that in situ generation of the aryl diazonium salt is compatible with anyl radical generation, cyclization, and trapping. The targeted cyclized iodide 2a was isolated in 68% yield (Table 1, entry 1). Yield was further improved by replacing NaI with KI (77%) and CsI (94%, entries 2 and 3) and 2a was obtained quantitatively when $Bu_4NI^{[8]}$ served as the iodide source (entry 4).^[9] Lowering the amount of Bu₄NI and nitrite led to reduced yields (entries 5 and 6). Surprisingly, tBuONO did not work well and a complex reaction mixture resulted (entry 7). The use of substoichiometric amounts of MeSO₃H provided a clean reaction but low conversion, showing that a stoichiometric amount of acid is necessary for complete conversion (entries 8 and 9). p-Toluenesulfonic acid worked almost as well as MeSO₃H; however, with CF₃COOH a lower yield was achieved (entries 10 and 11). The reaction can also be conducted in the presence of air, albeit a slightly lower yield was obtained (86%).

Under optimized conditions (Table 1, entry 4) the scope and limitations of the carboiodination using aryl amines as precursors were investigated (Figure 1). The preparation of all starting arylamines is described in the Supporting Information.



Figure 1. Alkyl iodides **2b–o** obtained by carboiodination of various aryl amines (isolated yields),^[a] Yield determined by ¹H NMR spectroscopy using an internal standard due to composition upon isolation.

Halides at the arene ring in the aryl amine are tolerated and iodides **2b**, **2c**, and **2h** were isolated in 88 to 99% yield. CF₃-, methyl-, and acetyl-substituted aryl amines work equally well and the corresponding cyclized dihydrobenzofurans **2e–g** were obtained in very good to excellent yields. However, reaction with the methoxy congener (see **2d**) was not as efficient (32%). As expected, the diastereoselectivity for the exocyclic trapping of the C radical was low and 2i was isolated in 90% yield as a 1.7:1 diastereoisomer mixture. We found a propargyl phenyl ether to cyclize in quantitative yield as determined by NMR spectroscopy. However, during isolation we realized that product 2j decomposes upon removal of the solvent.^[10] Formation of quaternary C centers is possible as shown by the preparation of 2k (54%). The corresponding 6-endo product was not identified in the crude reaction mixture. Indoline 21 and benzothiophene 2m were successfully prepared by application of our novel approach, showing that the method is not restricted to the preparation of O-heterocycles. Pleasingly, an excellent yield was also achieved in the 6-exo cyclization and iodide 2n was isolated in 97% yield. However, 7-exo cyclization of the aryl radical cannot compete with direct iodination under the applied conditions: aryl iodide 20 was obtained in 76% yield and the targeted cyclized product was not identified in the crude reaction mixture.

We next studied the 1,2-stereoinduction in the carboiodination using aryl amine **1p** as the substrate. Iodide **2p** was obtained in quantitative yield with 10:1 *trans/cis* diastereoselectivity (Scheme 2). A similar result was obtained in the reaction with aniline **1q**.



Scheme 2. Diastereoselective carboiodination.

We also investigated whether the intermediate cyclized radicals can be trapped by fast non-I-based radical-trapping reagents. Experiments were mainly conducted with **1a**. Bu_4NI was replaced by Bu_4NBr and Bu_4NCl ; however, the corresponding carbobromination and carbochlorination products were not formed. The diazonium salt derived from **1a** did not react with these halide sources.

Therefore, we continued to use Bu₄NI (1.5 equiv) for the clean generation of aryl radicals and added other typical C radical trapping reagents. Neither **2a** nor the carbobromination product **3a** was identified in the presence of *N*-bromosuccinimide (10 equiv). However, adding CBr₄ (10 equiv) under otherwise identical conditions gave the targeted bromide **3a** in 45% yield along with iodide **2a** in 18% yield (Scheme 3). Consequently, we increased the amount of CBr₄ to 30 equiv and obtained **3a** and **2a** in a 7:1 ratio. Unfortunately, combined yield decreased to 35% under these conditions. We therefore switched to other efficient alkyl-radical-trapping reagents and noted that in the presence of PhSeSePh (4 equiv) the carboiodination product **2a** was formed exclusively (50%).

PhTeTePh is known to be a highly efficient alkyl-radicaltrapping reagent.^[11] Indeed, after some optimization we found that when 4 equiv of PhTeTePh was added the



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Scheme 3. Carbobromination and carbotelluration.

telluration product **4a** was obtained in excellent yield (98%). Other carbotelluration products **4b**, **4e**, and **4g** were successfully prepared in moderate to excellent yields (43–78%) with this method. We found that in some cases the reaction works better with 2 equiv of PhTeTePh (see the Supporting Information). As expected based on our results reported above, high stereoselectivity was achieved for the cyclization of aniline **1q** to give the tellurated benzofuran **4q** in quantitative yield. The benzodihydrothiophene **4m** could be successfully prepared with this method, albeit in lower yield.

The suggested mechanism for the radical carboiodination and carbotelluration exemplified with substrate 1a is presented in Scheme 4. Arylamine 1a is first transformed with isoamyl nitrite in the presence of MeSO₃H to the diazonium salt 5a. Exchange of the anion in 5a with the anion of Bu₄NI provides diazonium iodide 5b. A literature search revealed only a single X-ray structure of an aryldiazonium iodide, indicating an interaction of the iodide anion with the terminal N atom of the diazonium group (Scheme 4).^[12] We therefore assume that the iododiazonium salt 5b is in equilibrium with its N-iododiazene form 5c. Considering structure 5c, initiation may occur by N-I homolysis to form I radical and radical **6a** which undergoes fast N_2 fragmentation to generate the aryl radical 7a. Alternatively, SET from the iodide to the diazonium cation also leads to 6a. 5-exo cyclization of 7a generates the alkyl radical 8a which likely abstracts an iodine atom from aryl-N=N-I (5c) to eventually give product 2a and the chain-carrying 6a. This I-atom-transfer step must be very fast and can only be suppressed with highly efficient radicaltrapping reagents. Moreover, successful trapping of 8a with external reagents such as CBr₄ and PhTeTePh shows that the trapping of 8a in the solvent cage with the I radical formed

Scheme 4. Suggested mechanism.

during initiation is not occurring. The I[•] radical can dimerize to I₂ which can also act as an alkyl-radical-trapping reagent. However, considering the low concentration of I₂ we currently disfavor I₂ or its adduct with an iodide anion (I₃⁻) as the trapping reagents. In the carbotelluration, cyclized radical **8a** is trapped by PhTeTePh to give tellurated product **4a**. The chain is likely sustained by I abstraction of the PhTe[•] radical from **5c**.

Finally, as an additional efficient radical-trapping reagent, we tested TEMPO in the I-induced cyclization reaction.^[13] Pleasingly, with 2 equiv of TEMPO under otherwise identical conditions TEMPO adduct **9a** was isolated in 89% yield starting with aniline **1a** (Scheme 5).^[14–16] In analogy, alkoxyamine **9r** was successfully prepared.

In summary, we introduced highly efficient and practical radical carboiodination reactions using aryl amines as substrates. Aryl amines are transformed in situ to the corresponding aryl diazonium salts which in turn act as aryl-radical



Scheme 5. Cyclizing carboaminoxylation.

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einheim www.angewandte.org These are not the final page numbers! precursors. Aryl radicals undergo typical 5-exo and 6-exo cyclization reactions and the cyclized alkyl radicals are then iodinated in a chain reaction. In the presence of PhTeTePh and TEMPO the cyclized radicals are efficiently trapped to provide the corresponding carbotelluration and carboaminoxylation products, respectively. Experiments are very easy to conduct and products are obtained in good to excellent yields.

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Communications



the corresponding aryl radicals, which are

products are obtained.

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