Regioselectivity

Iodonium Cation-Pool Electrolysis for the Three-Component Synthesis of 1,3-Oxazoles

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Abstract: The synthesis of 1,3-oxazoles from symmetrical and unsymmetrical alkynes was realized by an iodonium cation-pool electrolysis of I_2 in acetonitrile with a well-defined water content. Mechanistic investigations suggest that the alkyne reacts with the acetonitrile-stabilized I^+ ions, followed by a Ritter-type reaction of the solvent to a nitrilium ion, which is then attacked by water. The ring closure to the 1,3-oxazoles released molecular iodine, which was visible by the naked eye. Also, some unsymmetrical internal alkynes were tested and a regioselective formation of a single isomer was determined by two-dimensional NMR experiments.

1,3-Oxazoles are a well-studies class of heterocyclic compounds and several intra- and intermolecular synthetic approaches already exist.[1] The structural motif is present in numerous natural products (**1**),[2] pharmaceuticals (**2**),[3] chemicals for crop protection[4] and functional materials (**3**) so that a constant interest exist for further research in this area (Figure 1).[5]

To the best of our knowledge, an electrochemical synthesis from alkynes utilizing an iodonium-pool electrolysis has not been described before. However, an electrochemical approach for the synthesis of 1,3-oxazoles was reported by Waldvogel, using $ArIF_2$ as electrochemical generated reagent,[6a] as well as the electrosynthesis of benzoxazoles were reported by Waldvogel and Huang.[6b,c] Recent chemical methods for the synthesis of 1,3-oxazoles starting from alkynes and nitriles were described utilizing heterogeneous Au^I catalyst with *N*-oxides as a source of the oxygen,[6d] or via homogeneous Au^I catalysts.[6e] When cyanamides are used instead of nitriles with alkynes and *N*-oxides, the 2-amino-substituted 1,3-oxazoles are formed.[6f] In contrast, when ynamides are transformed with nitriles under $Yb(OTf)_3$ catalysis using *N*-iodosuccinimide as oxidizing agent and water as source of oxygen the corresponding 4-amino-substituted 1,3-oxazoles are generated.[6g] Also, catalytic amounts of hypervalent iodine compounds were applied with *m*CPBA as oxygen source and iodobenzene as catalyst[6h] or stoichiometric amounts of PhIO were used to generate the desired 1,3-oxazoles.[6i] A copper-catalyzed process, reported by Jiang utilized under oxygen (1 atm) and water as oxygen source was able to apply a number of nitriles and alkynes to generate the 1,3-oxazoles.[6j]

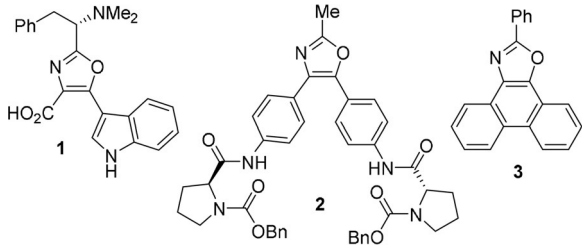

Figure 1. Selected examples of 1,3-oxazole-containing compounds.

In a recent study for the electrochemical arene TMS-iodine *ipso*-substitution,[7] we also performed a compatibility test[8] with other functional groups and alkynes proved to be not compatible with such a TMS-iodine exchange reaction. Further investigations were carried out on the reaction between alkynes and iodonium ions and the formation of an 1,3-oxazole was observed when cation-pool electrolysis in acetonitrile was performed. Based on the increasing general interest in electroorganic transformations,[9] we decided to investigate the electrochemical oxazole three-component synthesis from an alkyne in „wet" acetonitrile in more detail. We envisaged a transition-metal free electrochemical process starting from simple starting materials such as nitriles and alkynes, avoiding hazardous or sensitive starting materials or catalysts.

Several electrochemical parameters, such as the electrochemical cell design (divided/undivided), cation-pool versus direct electrolysis, supporting electrolyte (type and concentration), electrode material as well as other chemical parameters, such as the reaction temperature, the water content of the solvent were investigated.[10] The optimized reaction conditions are shown in Scheme 1, where the desired oxazole **5a** was obtained in quantitative yield.

From many optimization reactions, selected examples are summarized in Table 1 to exemplify the critical parameters for the successful oxazole synthesis of product **5a** (for more details, see the Supporting Information, S7–S9).

Initially, the content of water was investigated, and the optimal water content was determined to be around 1.0 equiva-

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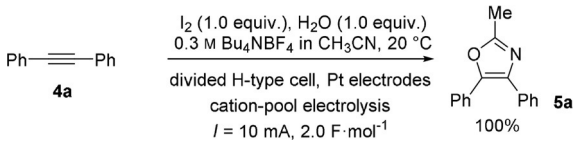


Scheme 1. Electroorganic cation-pool synthesis of 1,3-oxazole **5a**.

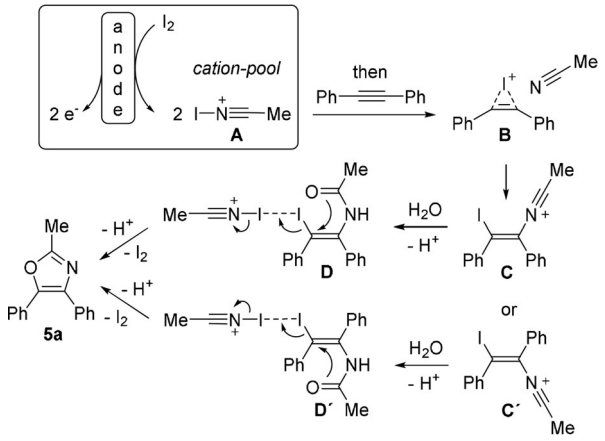
Table 1. Selected reactions performed during the optimization for the synthesis of **5a**.

No.[a]	Changes	Conversion [%]	Yield [%]
1	H_2O (0.5 equiv)	100	72
2	H_2O (1.0 equiv)	100	99
3	H_2O (1.5 equiv)	100	86
4	H_2O (2.0 equiv)	100	73
5	H_2O (3.0 equiv)	67	61
6	0.3 M $LiClO_4$	100	41[b]
7	0.3 M Bu_4NPF_6	100	61
8	0.1 M Bu_4NBF_4	94	82
9	0.5 M Bu_4NBF_4	93	89
10	carbon roving	100	70
11	glassy carbon	100	91
12	stainless steel (1.4571)	2	1[c]
13	NaI, 2.0 F mol^{-1}	48	34
14	direct vs. cation-pool electrolysis	99	38
15	temperature: 0 °C	100	86
16	temperature: 50 °C	90	57
17	current: 5 mA	86	71
18	current: 20 mA	100	93
19	1.0 F mol^{-1}	64	31
20	1.8 F mol^{-1}	100	94
21	2.3 F mol^{-1}	100	91
22	I_2 (1.0 equiv), no current	0	–
23	I_2 (1.0 equiv), acetamide (2.0 equiv)	0	–

[a] Yield determined by GC-FID using *n*-dodecane as internal standard. [b] Formation of benzyl as side-product was observed. [c] Only trace amounts of product could be detected.

lents (entries 1–5). Other supporting electrolytes besides Bu_4NBF_4 gave complete conversion as well, but inferior yields of **5a** and the best results were obtained with a 0.3 M solution (entries 6–9). Some other electrode materials, such as glassy carbon were also applicable and gave satisfactory results (entries 10–12). Also, the use of sodium iodide instead of I_2 in a cation-pool electrolysis gave only moderate results (entry 13)[11] and a direct electrolysis (in the presence of **4a**) resulted in complete conversion of the starting material. However, only a moderate yield of 38% of **5a** (entry 14) was obtained, most likely due to further electrochemical transformation of the oxazole product to several unidentified side-products. Furthermore, the reaction temperature, the current density and the amount of current is of importance to give good results (entries 15–21).[12] As can be seen from the control experiments (entries 22 and 23), the cycloaddition reaction is not initiated by I_2 alone, but electrochemical current must generate an acetonitrile-stabilized iodonium ion which is the primary initiator for the reaction. Also, acetamide did not undergo the reaction, so that an in situ hydrolysis of acetonitrile can be excluded.

Therefore, we conclude that the 1,3-oxazole synthesis is a stepwise reaction starting with the activation of the alkyne by acetonitrile-stabilized I^+ ions (iodonium ion **A**) which is followed by a Ritter-type reaction[13] where acetonitrile attacks the activated triple bond to generate a nitrilium ion **B**. Possibly, even in a concerted addition of the nitrilium ion to **B** the *Z*-isomer **C** or by a conventional *trans*-addition intermediate **C'** is formed. Nevertheless, these stabilized intermediates are attacked by water, deprotonated and ready for cyclisation resulting in a stepwise overall [2+2+1] cycloaddition process (Scheme 2).[6h]

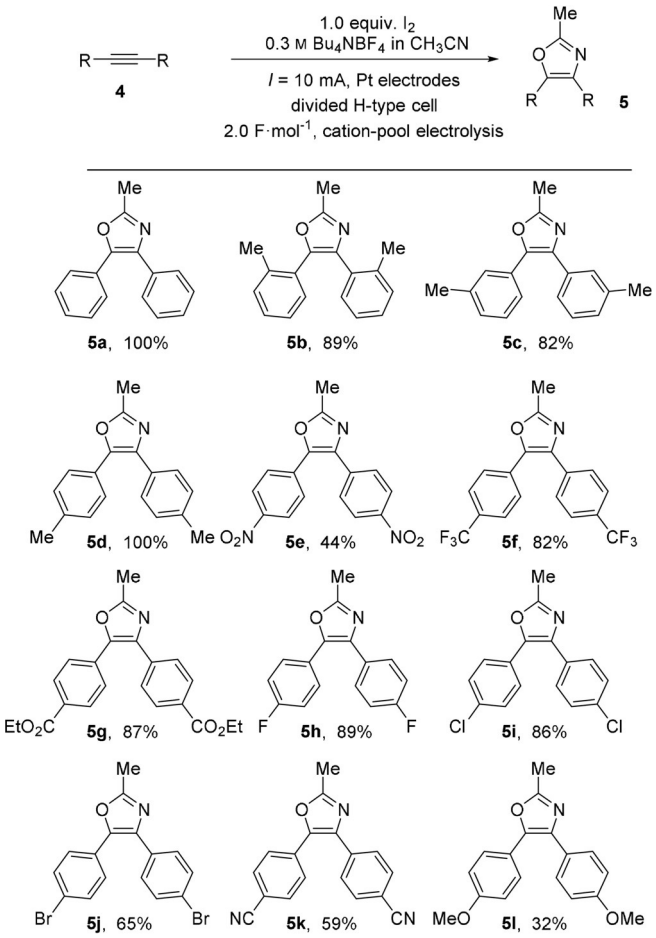


Scheme 2. Proposed reaction mechanism of the cation-pool electrolysis and the stepwise [2+2+1] cycloaddition process.

The formation of I_2 within a few minutes after the addition of the alkyne to the iodonium-pool indicates that the iodine atom in intermediate **C** is not simply liberated as an iodide anion by a nucleophilic substitution-type reaction but that a more complex reaction mechanism must be at work. For an optimal conversion and a high yield of the oxazole 2.0 F mol^{-1} of electricity must be used. This corresponds to a two-electron process per I_2 molecule and the formation of two I^+ ions. A rationale for this observation could be that the second iodonium ion is needed to interact with the iodine atom in intermediate **D** (or the *E*-configured intermediate **D'**) and forms a better leaving group, similar to the super-leaving group I-Ph in aryliodine(III) chemistry to initiate a S_N1-type substitution reaction.[6h,14] In rare occasions, intermediates of type **D**/**D'** (without the coordinated nitrilium reagent) were detected by GCMS in small amounts. However, isolation and characterization of these intermediates were not successful, and we were not able to determine whether the *E*- or the *Z*-configured iodoalkenylamides **D**/**D'** were formed. However, for the outcome of the reaction this seems to be of limited importance.

Under the optimized reaction conditions various symmetrical functionalized diaryl alkynes were reacted in acetonitrile under iodonium cation-pool conditions; the results are summarized in Scheme 3.

When the optimized reaction conditions for the formation of product **5a** were applied to other diaryl alkynes, good to excellent results were obtained. Additional methyl groups in *ortho*-, *meta*- and *para*-position were well tolerated (**5b**–**5d**;

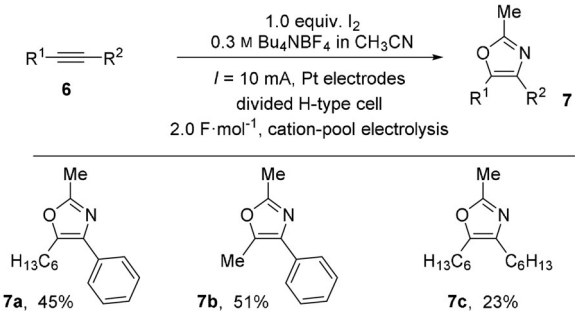


Scheme 3. Electroorganic iodonium cation-pool synthesis of oxazoles of type **5**.

82–100%) and electron-withdrawing groups, such as trifluoromethyl, ethyl ester and fluoro-substituents in *para*-position were also well accepted and gave the desired oxazoles in >82% yield (**5f**–**5h**). Only the 4-nitro group caused a diminished yield of only 44% (**5e**) which might not to be attributed to the electron-withdrawing effect but also to additional coordination of the iodonium ion to the nitro group. The 4-chloro- and 4-bromo-substituted derivatives were also applicable as well as the 4-cyano-substituted substrate (**5i**–**5k**) and only the electron-donating 4-methoxy derivative **5l** could be isolated in moderate 32% yield.

The transformation was not successful for electron-poor diethyl but-2-ynedioate (no conversion) as well as for terminal alkynes, such as phenylacetylene and the conjugated 1,3-diyne (1,4-diphenylbuta-1,3-diyne) led to several unidentified side-products. The utilization of a trimethylsilyl protected alkyne would have been another opportunity to apply terminal alkynes in this reaction. However, as was anticipated, the application of trimethylsilyl-substituted alkynes, such as trimethyl(*p*-tolylethynyl)silane, led to the iododesilylation instead of the formation of an oxazole product. The fact that an iododesilylation was observed additionally indicates that an iodonium cation-pool was generated electrochemically.

Finally, a selected small number of internal unsymmetrical alkyl-aryl alkynes and a dialkyl-substituted alkyne (**6**) were subjected to the electrochemically generated cation-pool to investigate if also alkyl sidechains are accepted. Furthermore, the major question was if the [2+2+1] cycloaddition would lead to a single regioisomer or if a mixture of regioisomeric oxazoles would be formed? The results for the iodonium cation-pool electrolysis and the reaction with these alkynes are summarized in Scheme 4.



Scheme 4. Results of the cation-pool electrolysis of unsymmetrical alkynes of **6a** and **6b** and the dialkyl-substituted alkyne **6c**.

Although the overall yields are only moderate for the alkyl-aryl-substituted alkynes, only single regioisomers (**7a** and **7b**) could be detected. In addition, the dialkyl-substituted oxazole **7c** was synthesized in a rather low yield of 23%. However, it became a valuable material for the structure determination of the regioisomers **7a** and **7b**.

The identity of the formed regioisomers was elucidated by recording two-dimensional $^{1}H/^{15}N$ correlation spectra of all three products (see supporting information, S43–S47). The results are shown in Figure 2.

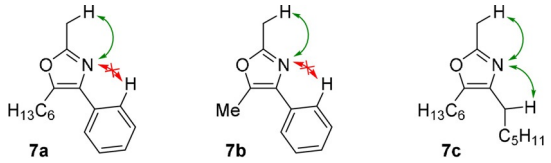


Figure 2. Results of the two-dimensional $^{1}H/^{15}N$ correlation NMR experiments and structure assignment of the compounds of type **7**.

The $^{1}H/^{15}N$ correlation spectra of **7a** only shows a single correlation signal for the methyl group derived from acetonitrile (^{3}J coupling) and no correlation signal for the *ortho*-protons (^{4}J coupling) of the phenyl ring. When oxazole **7b** was investigated, again only a single signal was detected. For the oxazole **7c** two signals were resolved in the $^{1}H/^{15}N$ correlation spectrum; one for the previous observed methyl group and one for the CH_2-group of the hexyl sidechain (both ^{3}J couplings). Therefore, we assigned the structures of **7a** to be the 2-methyl-5-hexyl-4-phenyloxazole and **7b** to be the 2,5-methyl-4-phenyloxazole regioisomer. The rationale for the formation of this re-

gioisomer goes back to the more stabilized cationic charge in benzylic position in an unsymmetrical iodonium species of type **B** (Scheme 2) which will favor the nucleophilic attack of acetonitrile in benzylic position.

In conclusion, we have realized an iodonium cation-pool electrolysis, which was applied for the synthesis of various 1,3-oxazoles from symmetrical alkynes in acetonitrile containing a well-defined amount of water. Also, a selected number of unsymmetrical alkynes were applied and a single regioisomer was formed, structure of which was determined by $^{1}H/^{15}N$ correlation NMR spectroscopy. The proposed mechanism explain the fact that two equivalents of the acetonitrile-stabilized iodonium cation are needed and that molecular iodine is visible within a few minutes after the addition of the alkyne.

Experimental Section

Both compartments of a divided cell were charged with 988 mg (3.00 mmol) Bu_4NBF_4 and in each compartment 10 mL of dry CH_3CN was added. Next, 1.0 equiv (0.500 mmol, 127 mg) iodine was dissolved in the anodic compartment and 15 equiv (7.52 mmol, 0.43 mL) acetic acid was added to the cathodic compartment. Last, 1.0 equiv (0.500 mmol, 9.01 μL) demineralized water was added to the anodic compartment. The platinum electrodes were submerged into the solution (active surface area: 1 cm^2) and a constant current of 10 mA was applied. After consumption of 2.0 F mol^{-1} (2 h 41 min), the electrolysis was stopped and 89.1 mg (0.500 mmol, 1.0 equiv) diphenylacetylene were added to the anodic compartment. The color of the solution turned immediately from bright red to violet within 5 min. The solution was stirred for 1 h and the conversion was determined by GCMS analysis. The solution of the anodic compartment was diluted with 15 mL CH_2Cl_2, 15 mL of aqueous saturated $Na_2S_2O_3$ and 15 mL of demineralized water were added, and the layers were separated. The aqueous layer was extracted three times with 15 mL CH_2Cl_2 each and the combined organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · cation-pool electrolysis · iodonium cation · oxazoles · regioselectivity

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