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Electrochemical Induced Ring Transformation of Cyclic α-(*ortho*-lodophenyl)-β-oxoesters

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Abstract: Cyclic α-(ortho-iodophenyl)-β-oxoesters were converted in ring-expanding transformation to furnish benzannulated cycloalkanone carboxylic esters. The reaction sequence started by electrochemical reduction of the iodoarene moiety. In a mechanistic rationale, the resulting carbanionic species was adding to the carbonyl group under formation of a strained, tricyclic benzocyclobutene intermediate, which underwent carbon-carbon bond cleavage and rearrangement of the carbon skeleton by retroaldol reaction. The scope of the reaction sequence was investigated by converting cyclic oxoesters with different ring sizes yielding benzocycloheptanone, -nonanone and -decanone derivatives in moderate to good yields. Furthermore, acyclic starting materials as well as cyclic compounds carrying additional substituents on the iodophenyl ring were submitted to this reaction sequence. The starting materials for this transformation are straightforwardly obtained bv conversion of β-oxoesters with phenyliodobis(trifluoroacetate).

Due to inherent entropic and enthalpic factors, the construction of seven-membered^[1] and larger (medium) sized rings^[2] defines a challenging task in synthetic organic chemistry. A common strategy towards such synthetic targets is the ring-expansion of more readily available compounds with five or six-membered rings.^[3] As an illustrative example, Stoltz and coworkers^[4] introduced the ring-expansion of β-oxoester 1a with an aryne furnishing benzocycloheptanone derivative 2a (Scheme 1). After addition of the enolate of oxoester 1a to the aryne, the reaction proceeds via intermediates 3 and 4. The aryne was generated in situ from trimethylsilylphenyltriflate and excess CsF. As alternative to this protocol we envisioned to generate carbanionic species 3 from iodo-compound 5a bv electrochemical reduction.^[5] Electrosynthesis is an attractive concept with steadily growing importance, because it can potentially reduce the amount of waste on one hand by avoiding spent redox reagents. On the other hand, renewable energy can be used to contribute to more sustainable conversions.^[6] The preparation of the starting materials of this new synthetic concept, α-(ortho-iodophenyl)-β-oxoesters 5, was recently introduced by Shafir and coworkers^[7] by conversion of βoxoesters 1 with PhI(O₂CCF₃)₂ (PIFA).

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))



Scheme 1. Previously reported ring-transformation of oxoester **1a** with an *in situ* generated aryne^[4] *via* intermediates **3** and **4**; entry into the same reaction sequence leading to product **2a** by electrochemical reduction of iodoarene **5a** (this work); and electrochemical ring-enlargement of oxoester **6** by cathodic reduction; conditions: 3 equiv. TMSCI, *n*Et₄NOTos, DMF, 23 °C, 0.2 A, 4 F mol⁻¹, Pb cathode, carbon anode.^[8]

We started the screening program for optimal reaction conditions based on a literature report by Shono et al. (Scheme 1), who have developed a cathodic ring-enlargement reaction of $\alpha\mbox{-}(bromomethyl)\mbox{-}\beta\mbox{-}oxoesters like compound 6 by application of$ DMF as solvent and 3 equiv. of TMSCI as additive to activate the carbonyl group of the ketone to facilitate the nucleophilic addition.^[8] As cathode material we have chosen leaded bronze, which was recently recommended as innovative material for reductive dehalogenations.^[9] Initially, we have used *n*Bu₄NClO₄ as conducting salt and a current of 10 mA and achieved 54% yield (Table 1, entry 1). Change of the conducting salt revealed that the anion had almost no influence on the yield. Other cations, however, lowered the yield. Therefore, we have chosen nBu₄NBr in all further experiments, since with this supporting electrolyte the byproduct profile was least complicated (entry 2). Variations of the cathode (graphite, glassy carbon, Cu, Pt, Pb) and anode (glassy carbon, Pt) materials did not improve the yields. Investigation of the Lewis acidic additive [TMSOTf, Ti(OEt)₄, TiCl₄, CeCl₃, LaCl₃, AlCl₃, InBr₃, ZnCl₂, Znl₂, BF₃ · OEt₂] gave also no improvements, however, without or with only 1

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equiv. TMSCI, no conversion was achieved, with 5 equiv. TMSCI the yield was lower. Survey of other solvents confirmed DMF to be optimal (MeCN, DMPU, NMP, and DMA gave lower yields, with 1,4-dioxane and THF no conductivity was achieved). The first and only significant improvement was achieved, when the electric current was lowered (entries 3 and 4). With 8 mA, 6.5 mA or 5 mA the yield raised to 71–72%. Upon further lowering (2.5 mA, entry 5) it dropped to 43%. In favor of a high reaction rate it was kept at 8 mA for all further optimizations. Variation of the reaction temperature (entries 6 and 7) as well as lowering the concentration of the conducting salt (entry 8) lowered the yield. For more details on the screening program see the Supporting Information.

Table 1. Selected examples of variation to the reaction conditions.



Entry	Change from initial conditions ^[b]	Yield of 2a ^[c]
1	no change	54%
2	nBu ₄ NBr (c = 0.3 mol L ⁻¹) as conducting salt ^[d]	55%
3	/=8 mA ^[e]	72%
4	/ = 6.5 mA or 5 mA	71%
5	/ = 2.5 mA	43%
6	$T = 0 \ ^{\circ}C$	36%
7	<i>T</i> = 40 °C	41%
8	$c(nBu_4NBr) = 0.2 \text{ mol } L^{-1}$	60%

[a] Reactions were performed in a divided cell on a 0.25 mmol scale with a substrate concentration of 36 mmol L⁻¹. [b] Initial conditions: 3.0 equiv. TMSCI, 0.3 mol L⁻¹ *n*Bu₄NCIO₄, DMF, 23 °C, 10 mA, 2.0 F mol⁻¹, CuSn₁₇Pb (leaded bronze) cathode, graphite anode. [c] Yield determined by GLC of the unpurified reaction mixture with mesitylene as internal standard. [d] This change was kept for entries 3–8. [e] This change was kept for entries 4–8.

With optimized reaction conditions in hand, we applied various substrates of type 5 to investigate the scope and limitations of the electrochemical induced rearrangement reaction. First, we have investigated the ring size of the starting materials (Table 2). Whereas the yield of the benzocycloheptanone 2a was good, it was somewhat lower for the benzannulated products with nine-(compound 2c, 64%) and ten-membered ring (2d, 45%). Attempts of converting the cyclohexanone derivative 5b to product 2b were never successful; instead, varying amounts of the protodeiodinated compound 8 could be detected in the reaction mixture. Interestingly, this type of starting material was also investigated by Stoltz in the aryne induced ring-expansion and the corresponding rearrangement was not observed as well in their investigation.^[4] The reason for this failure remains however unclear. Moreover, the conversion of indanone and tetralone derivatives 5e and 5f gave also rather complex reaction mixtures. However, in the latter case the desired

product dibenzocyclooctanone derivative 5f could be isolated in low yield (10%). The acyclic starting materials 5g and 5h could be converted to acetophenone derivative 2g (54%) and benzophenone derivative 2h (18%). Finally, cyclopentanone derivatives 5i–5m carrying additional substituents at the α -(ortho-iodophenyl)-moiety were prepared and converted to respective benzocycloheptanone derivatives 2i-2m. The yields range from 44% to 59% almost independently from the electronic nature and position of the additional residue. Interestingly, a fluoro substituent in compound 5j is tolerated adjacent to the proposed carbanionic center of the intermediate, thus, competing aryne formation seems not to take place, albeit product 2j was formed in 55% yield. While all these conversions were performed on a 0.25 mmol scale, we have performed the reaction of compound 5a also on a scale of 1 mmol and obtained product 2a with a slightly lowered yield of 56%, which might be due to the doubled concentration of the substrate 5a $(36 \text{ vs. } 71 \text{ mmol } L^{-1}).$

Table 2. Scope of the transformation with various α -(*ortho*-iodophenyl)- β -oxoesters **5**; yields refer to isolated and purified products.



[a] The reaction was performed on a 0.25 mmol scale. [b] The reaction was performed on a 1 mmol scale. [c] Protodeiodination product **8** was formed and isolated in 7% yield. [d] Unspecified decomposition.

The starting materials **5a–5g** of this study were accessed from the β -oxoesters **1a–g**^[10] following the original report^[7] with stoichiometric amount of PIFA (**9a**, R³ = H) and TFAA (trifluoroacetic anhydride) in a mixture of MeCN and TFA (trifluoroacetic acid; Scheme 2; see Supporting Information). An exception was compound **5h**, which was prepared by TiCl₄-mediated Claisencondensation from ethyl (2-iodophenylacetate) and benzoyl

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chloride.^[11] Compounds **5i–5m** were prepared accordingly from substituted PIFA-derivatives **9i–9m**. The latter were obtained by oxidation of the corresponding iodobenzene derivatives with oxone by following a literature protocol.^[12] As also observed by others,^[13] donor substituted PIFA reagents (e.g. with $R^3 = OMe$) cannot be obtained by this procedure.



Scheme 2. Preparation of starting materials 5a–5m from oxoesters 1a–1g and PIFA 9a and PIFA derivatives 9i–9m.

Regarding the mechanism of the overall transformation, it could be either proposed, that compound 5a is reduced to the corresponding phenyl radical, which then enters the reaction sequence by attack to the carbonyl group. More likely, however, is formation of a phenyl anion derivative (cf. species 3 in Scheme 1), which then proceeds to formation of the tricylic intermediate 4. As evidence for the latter process we have prepared the Grignard reagent from compound 5a by using a protocol introduced by Knochel et al. (Scheme 3)^[14] and indeed obtained the product 2a in 17% yield. Furthermore, when converting compound 5a to the respective phenyl radical by using *n*Bu₃SnH and AIBN, only the protodeiodinated product **10** could be detected by NMR. There is actually literature precedence on the electrochemical reduction of aryliodides. The initial electron transfer to a radical intermediate was reported to be relatively slow, while the second electron transfer to the anion was much faster.[15]



Scheme 3. Control experiments for the ionic or radical transformation of strating material 5a.

Crucial in the overall process seems the role of TMSCI. We propose it to activate the endocyclic carbonyl group (intermediate **11** in Scheme 4). Nucleophilic addition of the phenyl anion to the activated carbonyl group gives intermediate **12** with CO₂Et and OTMS groups in relative *cis*-configuration. The results of DFT-calculations at the M06-2X/Def2-TZVP level (see Supporting Information) revealed that this step is exergonic $[\Delta G^{298}(\mathbf{11} \rightarrow \mathbf{12}) = -268 \text{ kJ mol}^{-1}]$ and the reaction proceeds almost without barrier $[\Delta G^{298}^{\dagger}(\mathbf{11} \rightarrow \mathbf{12}) = +8 \text{ kJ mol}^{-1}]$. Initially, we had assumed that the TMS-group would then be transferred to the ester-oxygen while the C–C-bond is cleaved in the retro-

aldol reaction, thus the ketene-silyl acetal 13 would be formed. Although this process is slightly exergonic $[\Delta G^{298}(12 \rightarrow 13) = -6]$ kJ mol⁻¹], it is kinetically highly unfavorable. It should proceed via a transition state with a pentacoordinated silicon atom in a trigonal bipyramidal coordination environment where the two oxygen atoms adopt the axial positions. This arrangement cannot be realized within the strained tricyclic framework.^[16] Therefore we suggest, that the ring transformation is finalized after hydrolytic workup, which could be supported by calculations: The concerted ring-opening/proton-transfer reaction that yields the (Z)-isomer of enol 15 is essentially thermoneutral $[\Delta G^{298}(14 \rightarrow 15) = +1 \text{ kJ mol}^{-1}]$ and the subsequent exergonic tautomerization step drives the reaction to completion $[\Delta G^{298}(15 \rightarrow 2a') = -82 \text{ kJ mol}^{-1}]$. The proton transfer to the estercarbonyl oxygen atom is assisted by one water molecule, which allows the proton transfer to proceed via two hydrogen bridges with a relative small barrier $[\Delta G^{298} \ddagger (14 \rightarrow 15) = +61 \text{ kJ mol}^{-1}].^{[17]}$



Scheme 4. Mechanistic proposal for the transformation of compound 5a' by two-electron reduction in the presence of TMSCI to product 2a'. DFT calculations were performed at M06-2X/Def2-TZVP with the methyl instead of the ethyl esters; species 14, 15, and 2a' were calculated as hydrogen-bonded monohydrates.

In summary, a novel reaction pathway was realized for the generation of the oxo-esters of type **2** from iodobenzene derivatives **5** in the presence of TMSCI by a formal 1,3-acyl-shift. The reaction sequence starts by an electrochemical reduction of the iodobenzene derivative **5** and proceeds by nucleophilic addition of the carbanion to the carbonyl group followed by C–C

bond cleavage by retro-aldol reaction. From cyclic oxoesters as starting materials, a ring enlargement by two carbon atoms is achieved, thus elegant access to medium-sized ring compounds is attained.

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Conflict of Interests

The authors declare no conflict of interests.

Keywords: Annulation • Electrosynthesis • Medium-ring compounds • Reduction • Ring expansion

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