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Synthesis of 6-, 7-, and 8-membered lactones via the nickel-catalysed electrochemical arylation of electron-deficient olefins

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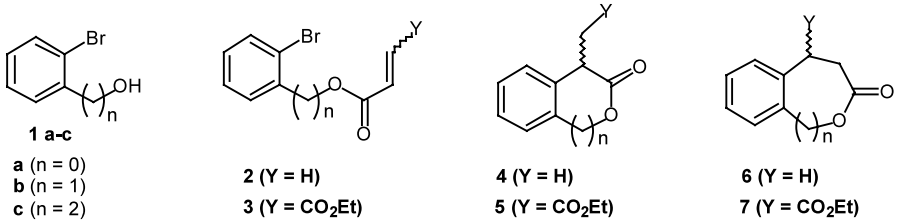
Abstract—A nickel-catalysed electroreductive process of arylation of α,β-unsaturated carboxylic esters has been applied to the synthesis of medium-sized lactones. Of the two possible approaches investigated in this study, the most efficient one involves first the electrochemical condensation, followed by the lactonisation.

The last two decades have seen a great upsurge of new electroreductive C,C-bond forming reactions by direct or indirect coupling reactions between organic halides and various electrophiles. Not much attention has been paid, however, to the application of these reactions to the formation of cyclic compounds. The scarce examples of such ring forming reactions have been reviewed.[1] We thus decided to explore the scope and limitations in ring formation of some electrochemical reactions developed in these laboratories in connection with the use of both the sacrificial anode process and the nickel-complex catalysis. We have started this investigation with one of the most efficient electroreductive processes, i.e. the arylation of activated olefins,[2a–c] with the aim of forming lactones or lactams.

The nickel-catalysed electrochemical arylation of electron-deficient olefin is easily conducted at 60–70°C without the need of separate preparation of any organometallic intermediate. This reaction is also characterised by high efficiency and large functional tolerance. The reaction mechanism has already been discussed in a previous paper.[2b] Our first approach, referred to as route A, was based on the general method already used in the formation of cyclic compounds,[1] involving an aryl halide tethered to an acrylic or fumaric moiety through an ester or amide function. Such a structure should, at first, lead to an efficient ring formation by intramolecular arylation of the C,C-double bond (Scheme 1). We then have prepared a few structures (**2 a**–**c** and **3 a**,**b**) by esterification with the



Scheme 1.

Keywords: lactones; nickel catalysis; electroreduction; conjugate addition.

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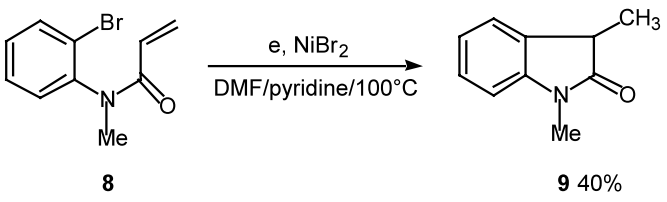


Scheme 2.

desired acyl chloride of commercially available phenyl bromides (**1a**–**c**) bearing an alcohol group attached to the ring in the *ortho* position, either directly ($n=0$), or tethered by one or two methylene groups ($n=1$ or 2). The cyclisation reactions were conducted in DMF/pyridine (9/1) at 100°C with catalytic quantities of $NiBr_2$ as catalyst precursor, using an undivided electrolytic cell fitted with an iron anode and a nickel-foam cathode. A constant current intensity of $I=0.05$ A was applied until full consumption of the starting reagent.[3]

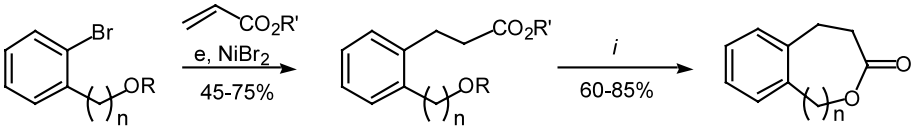
Actually, the results obtained by this route are not satisfactory. On the one hand, with compounds **2** we could obtain only the formation of the 6-*endo*-cyclisation product dihydrocoumarine **6a** from **2a** in 40% yield. Compounds **2b** and **c** were transformed into a mixture of reduced products, i.e. resulting from the reduction of the carbon–bromine bond and/or of the C,C-double bond. On the other hand, from compound **3b**, only the 6-*exo*-cyclisation product **5b** was obtained but in a low 20% yield.[4] A mixture of reduction products was obtained from **3a**. It therefore becomes clear that this approach is not general at all, and that, despite the intramolecular nature of the cyclisation process, critical factors like the length of the arm bearing the olefin moiety or the substitution pattern on the double bond may restrict dramatically the scope of this synthetic route.

We turned to the nitrogen compound **8**, and found that in this case the 5-*exo*-cyclisation product **9**[5] was obtained in 40% yield (Scheme 2) along with traces of 6-*endo*-cyclisation. This pattern of cyclisation has already been observed in a similar structure.[6] On the other hand the reduction products were obtained from the starting compound having a fumaric structure attached to the nitrogen.

Because of the limitations encountered in the intramolecular method (route A) we decided to try another approach which consists in making first the C,C-bond by bimolecular coupling between *ortho*-substituted aryl halides and esters of acrylic acid (Scheme 3), followed by the lactonisation step (route B). This requires that no major steric effect of the *ortho*-substituent would prevent the arylation reaction.

We started investigating this new route with *ortho*-bromoanisole **10a** and methyl or *n*-butyl acrylate, and found that **12a** was formed in relatively good yield (50%). The reaction conditions were similar to those used in the previous approach.[3] We thereafter extended the reaction to the two other reagents with $n=1$ or 2 after having protected the hydroxyl group[7] in the form of either a methyl ether (**10b**,**c**) or a THP acetal (**11b**,**c**).[8] Compounds **12b** and **c** were obtained in 45 and 75%, respectively, and compounds **13b** and **c** in 58 and 46%. It is remarkable that this bimolecular coupling reaction is not so sensitive to the possible *ortho*-steric effect. In addition, we did not try so far to optimise these arylation reactions.

With compounds **12** and **13** in hand, we had next to perform the cyclisation. Many methods have been published on lactone formation,[9] and we tried to select the most simple and efficient one with regards to the expected ring-size, and having in mind that the two functions, the ether and the ester groups, have to be cleaved, and possibly with the same reagent. We first tried BBr_3,[10] which is usually used at low temperature, and we efficiently applied it to the formation of dihydrocoumarine **6a** in 85% from **12a**. However, with **12b** and **c**, the action of BBr_3 led to the methylether–halogen exchange instead of the lactone formation. That is the reason why we replaced the ether protecting group in **10** by THP to obtain **13b** and **c**. Starting from **13b** and **c**, the corresponding lactones **6b**[11] and **c**[12] were obtained in 62 and 60%, respectively, by treatment with MeOH/KOH at reflux. It may be worth noting that this approach, illustrated in Scheme 3, and referred to as route B, gives only one mode of attachment between the two moieties at the β-carbon of the activated C,C-double bond, which actually corresponds to the *endo*-cyclisation mode in the previous approach in the final product **6**.



10 (R = Me) a-c
11 (R = THP) b,c
a (n = 0)
b (n = 1)
c (n = 2)

12 (R = Me)
12a: 50%
12b: 45%
12c: 75%

13 (R = THP)
13b: 58%
13c: 46%

6a: 85%
6b: 62%
6c: 60%

i: see text

Scheme 3.

In summary, we have explored two routes to prepare medium-sized lactones based on the electrochemical arylation of activated olefins catalysed by a nickel complex. The route based on the intramolecular C,C-bond formation does not seem to be general enough, at least in the selected reaction conditions. We have however found an interesting alternative which is based on the bimolecular coupling between an *ortho*-substituted aryl halide and an α,β-unsaturated ester, followed by the lactonisation.

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3. **Typical electrochemical procedure**: The undivided cell was equipped with a nickel foam (15 cm^2) as the cathode and an iron rod as the anode. A short electrolysis was first conducted at constant current intensity (0.15 A) and at room temperature for 30 min with the (9/1) DMF/pyridine solution containing tetrabutylammonium bromide (200 mg) as supporting electrolyte and 1,2-dibromoethane in order to generate a small amount of iron ions. After the addition of $NiBr_2{\cdot}3H_2O$ (20% vs aryl halide) and the reagent (route A) or the mixture of reagents (route B), the electrolysis was run at constant current intensity (0.05 A for route A, 0.15 A for route B) at 100°C. After usual work-up, the product was isolated by column chromatography on silica gel (230–400 mesh) using pentane/ether as eluent. The products were fully characterised by ^1H NMR, ^{13}C NMR, MS and IR analysis.
4. **5b** (20%): ^1H NMR (200 MHz, $CDCl_3$): δ 7.3–7.0 (m, 4H), 5.45–5.3 (2d, AB system, 2H, $J=13.8$ Hz, $\Delta\nu/J=2.63$), 4.25 (q, 2H, $J=7$ Hz), 4.1 (m, ABX, 1H), 3.2–3.1 (m, ABX, 2H, $J=16.91$, 6.59, 6.37, $\Delta\nu/J=2.38$), 1.3 (t, 3H, $J=7$ Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 171.8, 171.3, 133.1, 132.0, 128.8, 127.3, 124.9, 124.0, 69.3, 61.0, 41.1, 32.4, 14.0; MS (EI) m/z (rel. intensity): 234 (5), 188 (100), 160 (56), 146 (13), 115 (31), 103 (6), 91 (8); IR (KBr) ν (cm^{-1}): 3015, 2931, 1735, 1601, 1580.
5. **9** (40%): ^1H NMR (200 MHz, $CDCl_3$): δ 7.2–6.7 (m, 4H), 3.3 (q, 1H, $J=7.6$ Hz), 3.1 (s, 3H), 1.37 (d, 3H, $J=7.6$ Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 178.6, 143.8, 130.5, 128.7, 123.3, 122.3, 107.8, 40.4, 26.0, 15.3; MS (EI) m/z (rel. intensity): 161 (100), 146 (46), 132 (26), 118 (70), 91 (24), 77 (5), 65 (4), 51 (5); IR (KBr) ν (cm^{-1}): 3014, 2936, 2253, 1702, 1615, 1494, 1351.
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11. **6b** (62%): ^1H NMR (200 MHz, $CDCl_3$): δ 7.3–7.0 (m, 4H), 3.4 (s, 2H), 2.9 (dd, 2H, $J=8.1$, 7.5 Hz), 2.5 (dd, 2H, $J=8.1$, 7.5 Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 173.6, 140.2, 139.6, 129.5, 128.9, 128.0, 126.8, 62.6, 35.5, 27.7; MS (EI) m/z (rel. intensity): 162 (30), 144 (26), 133 (20), 134 (6), 118 (21), 117 (100), 105 (18), 91 (46); IR (KBr) ν (cm^{-1}): 3030, 2980, 1731, 1600, 1580.
12. **6c** (60%) mp 61–62°C: ^1H NMR (200 MHz, $CDCl_3$): δ 7.0 (s large, 4H), 3.7 (t, 2H, $J=7.2$ Hz), 2.8–3.0 (m, 4H), 2.5 (m, 2H); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 180.7, 143.8, 141.5, 134.9, 133.9, 131.5, 131.4, 68.0, 40.6, 40.1, 32.5; MS (EI) m/z (rel. intensity): 176 (32), 161(7), 146 (88), 131 (51), 117 (30), 104 (100), 91 (73), 78 (31); IR (KBr) ν (cm^{-1}): 3014, 2980, 1712, 1492.