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Tetrahedron 63 (2007) 3006–3009

Tetrahedron

Selective radical cyclisation of propargyl bromoethers to tetrahydrofuran derivatives via electrogenerated nickel(I) tetramethylcyclam

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Received 8 December 2006; revised 25 January 2007; accepted 31 January 2007
Available online 3 February 2007

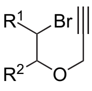
Abstract—The controlled-potential reduction of [1-bromo-2-methoxy-2-(prop-2′-ynyloxy)ethyl]benzene (**1a**), 1-[2-bromo-2-phenyl-1-(prop-2′-ynyloxy)ethyl]-4-methoxybenzene (**1b**) and 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxypropanamide (**1c**) catalysed by (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(I), $[Ni(tmc)]^+$, at a vitreous carbon cathode in DMF/Et_4NBF_4 leads to 2-methoxy-4-methylene-3-phenyl-tetrahydrofuran (**2a**), 2-(4′-methoxyphenyl)-4-methylene-3-phenyl-tetrahydrofuran (**2b**) and 2-(3′,4′-dimethoxyphenyl)-3-carbamoyl-4-methylenetetrahydrofuran (**2c**), respectively, in very high yields.

1. Introduction

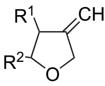
Owing to their widespread presence in nature as well as their breadth of biological activity, lignans have attracted considerable attention from organic chemists.[1] Some lignans exhibit anti-tumour activity, whereas others function as diuretic, analgesic and anti-rheumatic compounds. A major subgroup of lignans is comprised of tri- and tetra-substituted tetrahydrofurans the synthesis of which poses interesting and often unsolved problems of stereocontrol.

Radical cyclisation continues to be a central methodology for the preparation of natural products containing heterocyclic rings.[2,3] A majority of radical cyclisations in heterocyclic chemistry are still accomplished with the aid of tri-*n*-butyltin hydride, Bu_3SnH,[4] and such synthesis typically involves the use of an excess of Bu_3SnH in the presence of a small amount of radical initiator, usually azobisisobutyronitrile (AIBN). For example, the synthesis of a furofuran lignan, isogmelinol,[5] has been accomplished by means of tri-*n*-butyltin hydride, but tin hydrides are toxic and troublesome to separate from the desired products. A convenient alternative is the use of electrogenerated macrocyclic nickel(I) complexes as mediators for reductive intramolecular cyclisations.[6–28] Many studies have used cyclic voltammetry to establish that (a) the nickel(I) complexes are readily produced in aprotic media by a reversible $1e^-$ reduction of the corresponding nickel(II) complex, (b) the nickel(I) complexes react with a range of unsaturated alkyl halides to produce radical intermediates that can undergo cyclisation with the nickel(II) complex being reformed and (c) these electrocatalytic reductions occur at a potential where the alkyl halides themselves do not undergo reduction.

A recent paper[26] from our laboratory has reported the catalytic reduction of the propargyloxy derivatives **1a**–**1c** by electrogenerated $[Ni(tmc)]^+$.

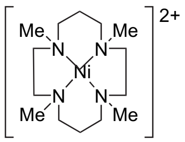


1



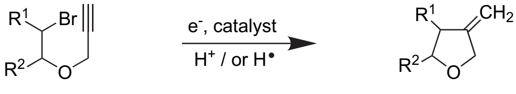
2

a: R^1 = phenyl; R^2 = methoxy
b: R^1 = phenyl; R^2 = 4-methoxyphenyl
c: R^1 = $CONH_2$; R^2 = 3,4-dimethoxyphenyl



$[Ni(tmc)]Br_2$

The constant-current electrolyses described, however, led only to moderate yields of the desired products, the tetrahydrofuran derivatives, **2a**–**2c** (Eq. 1).



1 **2** (1)

Side reactions led to other products. In particular, the exocyclic derivative **3** was found to isomerise in the presence

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Keywords: Electrosynthesis; Electrocatalytic reduction; Intramolecular cyclisation; Nickel(I) tetramethylcyclam.

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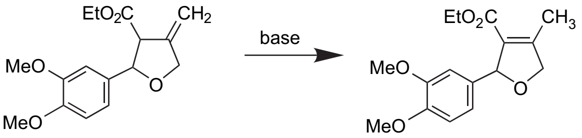
doi:10.1016/j.tet.2007.01.071

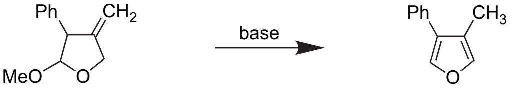
of cathode generated base to give the dihydrofuran **4**[27] (Eq. 2):



3 **4**

(2)

while with appropriate substituents, for example, **1a**, further reaction to the corresponding furan **5** was observed[26] (Eq. 3):



1a **5**

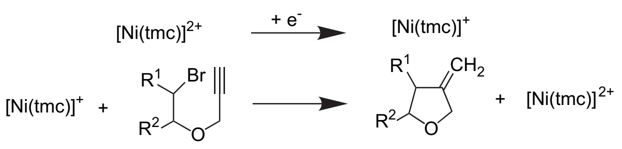
(3)

With related substrates, the cleavage of the carbon–oxygen bond[26] also produced byproducts.

This paper reports the development of a synthetic procedure where the propargyloxy derivatives **1a–1c** could be converted selectively to the corresponding tetrahydrofuran compounds, **2a–2c**.

2. Results

Using cyclic voltammetry we have shown in earlier studies that, in *N*,*N*′-dimethylformamide (DMF) containing 0.1 M Et_4NBF_4, $[Ni(tmc)]^{2+}$ undergoes a reversible one-electron reduction to the stable $[Ni(tmc)]^+$ species and the formal potential for the Ni(II)/Ni(I) couple is −0.86 V versus an Ag/AgCl/aqueous 3 M KCl reference electrode.[27] The substrates **1a–1c** reduce directly at potentials below −1.60 V. While similar potentials would be observed with other macrocyclic nickel(II) complexes, $[Ni(tmc)]^{2+}$ has the advantage that the catalytic cycle is rapid. This is seen[26,27] by the large cathodic peaks on cyclic voltammograms for solutions containing $[Ni(tmc)]^{2+}$ and an excess of substrate (the increase in peak current for the Ni(II) complex reduction is a measure of the rate at which the complex is regenerated and hence the complete catalytic cycle is rapid) and it leads to the possibility of quick synthetic electrolyses with only a catalytic amount of the nickel(II) complex.



Controlled-potential electrolyses were carried out at approximately −0.90 V versus Ag/AgCl (in fact, 100 mV more negative than the voltammetric peak potential for the reduction of $[Ni(tmc)]^{2+}$ in the presence of the substrate) using both Pt gauze and reticulated vitreous carbon cathodes for mixtures of $[Ni(tmc)]^{2+}$ and each of the substrates **1a–1c** in DMF/0.1 M Et_4NBF_4. The results are reported in Table 1. It can be seen that with each substrate, electrolyses were carried out with different ratios of catalyst to substrates and in the presence and absence of a proton donor, 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 1. Coulometric data and product yields for catalytic reduction of **1a–1c** by $[Ni(tmc)]^+$ electrogenerated at platinum cathodes and reticulated vitreous carbon cathodes in DMF containing 0.10 M Et_4NBF_4

Entry	$[Ni(tmc)]^{2+}$, mM	[**1**], mM	[HFIP], mM[a]	*n*[b]	Product yield, %[c]
RBr=[1-bromo-2-methoxy-2-(prop-2′-ynyloxy)ethyl]-benzene (**1a**)					**2a**
1[d]	0.4	2.1	—	1.1	80
2[d]	0.4	4.0	—	1.0	84
3	0.9	1.8	3.6	1.1	79
4	0.9	1.8	6.5	1.2	86
5	0.8	1.7	16.0	1.1	79
RBr=1-[2-bromo-2-phenyl-1-(prop-2′-ynyloxy)ethyl]-4-methoxybenzene (**1b**)					**2b**
6[d]	0.4	1.9	—	1.0	100
7[d]	0.4	4.0	—	1.1	98
8	0.9	1.8	3.5	1.0	80
9	0.8	1.7	6.5	1.1	95
10	0.9	1.7	16.0	1.1	87
RBr=2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxypropanamide (**1c**)					**2c**
11[d]	0.5	2.1	—	0.9	89
12[d]	0.3	3.4	—	1.1	99

[a] HFIP=1,1,1,3,3,3-hexafluoro-2-propanol.
[b] Number of electrons *per* molecule of starting material **1**.
[c] Yield expressed as the percentage of **1** incorporated into each product.
[d] Reticulated vitreous carbon cathode.

It can be seen that in all electrolyses, the yields (as determined by gas phase chromatography) of the desired products, the tetrahydrofuran derivatives **2a–2c**, were excellent and the yields were unaffected by the presence of the proton donor. Although the yields of the species **2a–2c** are less than 100% in some experiments, we found no evidence (e.g., additional gas chromatographic peaks) for any other product. Furthermore, when the ratio of catalyst to substrate was only 0.1 we observed that all reactions went to completion.

The initial current densities were high, in fact, a significant fraction of the expected values assuming mass transport control by the substrate (although higher for **1a** and **1b** than for **1c**). This allows for a rapid electrolysis. Moreover, the currents dropped smoothly with time and the charge consumed before the current dropped to a background level, allowed for an estimation of the number of electrons (*n*) involved in the reduction of the substrate. In all electrolyses, the reaction involves $1e^-$/molecule of substrate. The high surface area material, reticulated vitreous carbon, is the preferred cathode. Electrolyses were faster and the Pt electrodes were found to passivate when the ratio [substrate]/[Ni(II)]>2. It was then necessary to clean the electrode at intervals in order to complete the electrolysis.

3. Discussion

It is clear that controlled-potential electrolysis in the presence of a catalytic quantity of the square planar nickel(II) complex is a selective and convenient way to convert the brominated propargyloxy derivatives, **1a–1c**, into the corresponding tetrahydrofuran derivatives, **2a–2c**. The conversions are also carried out at room temperature and in an environmentally friendly procedure.

The coulometry in the absence of any influence of proton donor demonstrates that the reaction proceeds via radical intermediates. In fact, according to Halcrow and Christou,[29] who published an extensive review of catalytic processes involving nickel(I) complexes and alkyl halides, a nickel(I) species can transfer one electron to an alkyl halide via an inner-sphere mechanism and an alkylnickel intermediate might be formed. The subsequent decomposition of the alkylnickel intermediate could generate alkyl radicals. The radical intermediate resulting from the cleavage of the C–Br bond undergoes rapid intramolecular cyclisation to give the carbocyclic radicals that then extract a H atom from the solvent to form the final products. There is substantial evidence in the literature that DMF can act as a hydrogen atom donor[30–33] and the DMF radical formed can only be reduced at much more negative potentials,[34,35] approximately -1.95 V versus SCE.

With respect to the stereochemistry of the starting materials and of the cyclic products, it should be noted that the original trans R^1-to-R^2 group orientation of compounds **1b** and **1c** is retained in **2b** and **2c**, respectively, but the original mixture of isomers of compound **1a**, in which R^1-to-R^2 groups are cis and trans to each other in a 80:20 ratio, afforded **2a** as a single trans stereoisomer, according to NMR and by comparison with an authentic sample.

It is apparent that the yields of the tetrahydrofuran derivatives are much higher than in our earlier work[26] and the byproducts reported there were not formed. In the controlled-current electrolysis, it was necessary to pass much higher charge in order to complete the conversions and this charge was leading to the formation of bases close to the cathode surface.[36] The basic species were reacted with the tetrahydrofurans to give the byproducts.

4. Experimental section

4.1. Reagents

Each of the following chemicals was used as received: nickel(II) bromide (Aldrich, 98%), 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam (tmc), ACROS, 97%), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, Aldrich, 99.8+%), *n*-tetradecane (Aldrich, 99+%) and *n*-hexadecane (Aldrich, 99+%). Dimethylformamide (DMF), ‘distilled-in-glass’ reagent from Aldrich, was used as received. We obtained tetraethylammonium tetrafluoroborate ($TEABF_4$) with a purity of 98% from Fluka and it was stored in a vacuum oven at 80 °C to remove traces of water. Deaeration procedures were carried out with zero-grade argon (Air Products).

Published procedures were employed for the preparation of $[Ni(tmc)]Br_2$,[37] [1-bromo-2-methoxy-2-(prop-2′-ynyloxy)ethyl]benzene (**1a**),[5] 1-[2-bromo-2-phenyl-1-(prop-2′-ynyloxy)ethyl]-4-methoxybenzene (**1b**)[5] and 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxypropanamide (**1c**).[38] Synthesis of 2-methoxy-4-methylene-3-phenyl-tetrahydrofuran (**2a**), 2-(4′-methoxyphenyl)-4-methylene-3-phenyltetrahydrofuran (**2b**) and 2-(3′,4′-dimethoxyphenyl)-3-carbamoyl-4-methylenetetrahydrofuran (**2c**) was based on the method published by McCague et al.[39]

4.2. Electrochemical experiments

Electrodes for cyclic voltammetry were fabricated from 3 mm diameter glassy carbon rods (Tokai Electrode Manufacturing Company, Tokyo, Japan, Grade GC-20), press-fitted into Teflon shrouds to provide planar, circular working electrodes with areas of 0.08 cm^2. Before use, the electrodes were cleaned with an aqueous suspension of 0.05-μm alumina (Buehler) on a Master-Tex (Buehler) polishing pad. Working electrodes for controlled-potential electrolyses were a Pt gauze (area 2.4 cm^2) and or a reticulated vitreous carbon disk (0.2 cm in thickness, 2.4 cm in diameter, and approximately 100 cm^2 in real area) (RVC 2X1-100S, Energy Research and Generation, Oakland, CA). Procedures for cleaning and handling of these electrodes have been described previously.[40]

All potentials are quoted with respect to a Ag/AgCl/3 M KCl in water reference electrode.

Cells for cyclic voltammetry[41] and for controlled-potential electrolysis[42] have been described in earlier publications. For the controlled-potential electrolyses the working and counter electrodes were separated by a glass sinter. The counter electrode was a Pt gauze or graphite rod.

Cyclic voltammograms were obtained and controlled-potential electrolyses were carried out with the aid of an AUTOLAB model PGSTAT12 potentiostat–galvanostat. The data from the above experiments were acquired and stored by locally written software, which controlled a data acquisition board installed in a personal computer.

^1H NMR data were recorded on a Varian Unity Plus 300 Spectrometer in $CDCl_3$; δ (parts per million) was measured versus residual peak of the solvent. Identities of the electrolysis products were confirmed by means of a Hewlett–Packard 5890 Series II gas chromatograph coupled to a Hewlett–Packard 5971 mass-selective detector.

4.3. Identification and quantification of products

Gas chromatographic analyses were accomplished with the aid of a Chrompack, type CP 9000, instrument equipped with flame ionisation detector. Products were separated with a 25 m×0.25 mm i.d. capillary column (WCOT fused silica) with a stationary phase of poly(methylphenylsiloxane). A known quantity of an electroinactive internal standard (*n*-hexadecane or *n*-tetradecane) was added to a solution before each experiment to allow quantitative determination of the electrolysis products. Gas chromatographic response factors were measured experimentally with authentic samples of each product, and all product yields tabulated in this paper represent the absolute percentage of starting material incorporated into a particular product. In order to isolate the products, the DMF solvent was evaporated under vacuum, the reaction mixture hydrolysed with 0.1 M HCl saturated with NaCl, up to pH 1–2, extracted with CH_2Cl_2 and washed with H_2O. The dried ($MgSO_4$) organic layer was evaporated. The crude residue was submitted to flash chromatography over silica gel (230–400 mesh) using diethyl ether/light petroleum 1:2 (for **2a**), diethyl ether/light petroleum 1:3 (for **2b**) and ethyl acetate/methanol 13:1 (for **2c**) as eluants.

Identities of the major products (**2a**–**2c**) derived from controlled-potential electrolyses were confirmed by comparison of gas chromatographic retention times as well as ^{1}H NMR and mass spectra for the isolated products[26] with those of the authentic compounds.

Acknowledgements

The authors would like to thank Professor D. Pletcher for comments and helpful discussions. We are grateful to the FCT/FEDER (POCTI/QUI/37808/01) and to the Fundação Calouste Gulbenkian for financial support of this work.

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