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One-Pot Assembly of Tricyclo[6.2.1.0^{1,6}]undecan-4-one and Related Polycyclic Compounds by Tandem Electroreductive Cyclization

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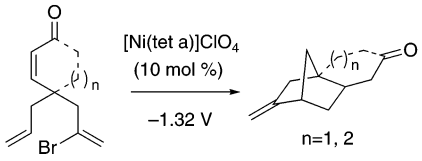
ABSTRACT



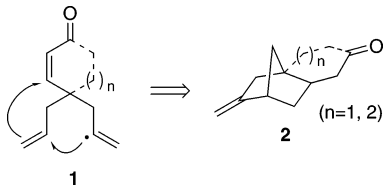
Electroreductive tandem cyclization of 4-allyl-4-(2-bromoprop-2-en-1-yl)cyclohex-2-en-1-one to tricyclo[6.2.1.0^{1,6}]undecan-4-one has been demonstrated. This protocol represents an attractive alternative to conventional tandem radical cyclization.

The assembly of polycyclic molecules through carbon−carbon bond-forming processes in a single operation is a significant direction for organic synthesis. Therefore, various types of tandem reactions have been actively developed in recent years. In fact, this field is mostly dominated by the employment of transition-metal chemistry and radical processes.[1] The advantage of these methods over conventional reactions is that they proceed under mild conditions and involve simple manipulation. However, they suffer from drawbacks resulting from the high cost of the transition metals and from concerns about toxicity of tin species. In view of increasing strict environmental legislation, the creation of toxicologically benign and environmentally friendly methodologies has become attractive.[2]

As part of our studies on the discovery and development of new tandem reactions,[3] we herein report a strategy based on intramolecular electroreductive cyclization. Since electrochemical processes only use electrons as a reagent, they have received increasing attention in recent years.[4]

The sequence of electroreductive cyclizations outlined in Scheme 1 provides a route to tricyclo[6.2.1.0^{1,6}]undecane-4-one and related polycyclic compounds. Vinyl radical **1**, resulting from the corresponding bromide by means of cathodic reduction, could consecutively cyclize onto the appropriate unsaturated side chain and enone to form a bridged tricyclic ring system **2**.[5]

Scheme 1. Synthetic Plan



(1) For recent reviews, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224. (b) Poly, G.; Giambastiani.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (d) Little, R. D. *Chem. Rev.* **1996**, *96*, 93.

(2) Tundo, P.; Anastas, P.; Black, D. StC.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207.

(3) (a) Toyota, M.; Yokota.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856. (b) Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627. (c) Toyota, M.; Yokota, M.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1551.

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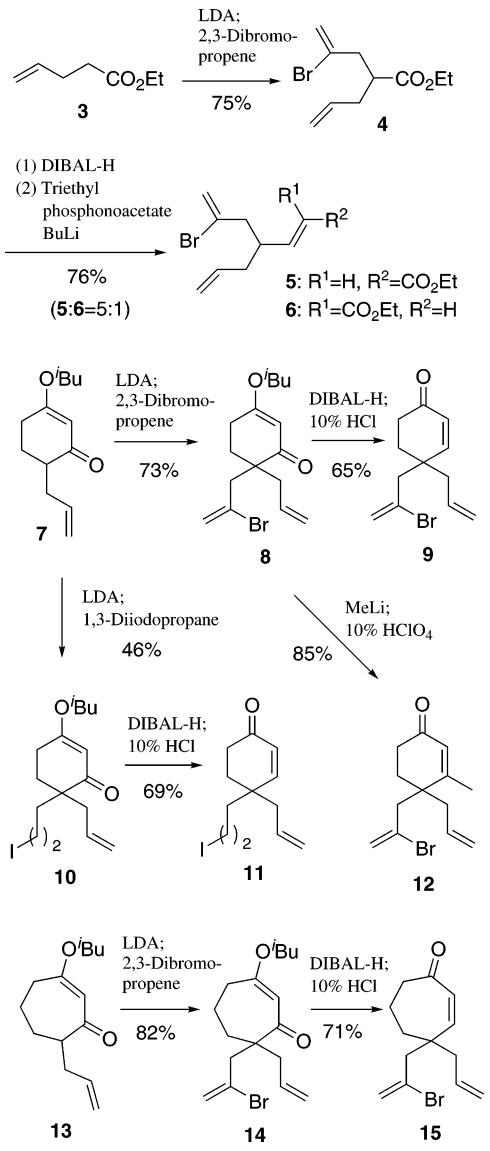
Prior to testing the feasibility of the envisaged protocol, the requisite substrates were prepared as depicted in Scheme 2. Namely, *E*-olefin **5** and *Z*-olefin **6** were synthesized from

Scheme 2. Preparation of Key Substrates



ethyl 4-pentenoate (**3**) by alkylation followed by DIBAL-H reduction and Wadsworth−Emmons olefination. Silica gel chromatography achieved the separation of **5** and **6**. Enone **9** was next prepared from compound **7** using Stork−Danheiser's protocol.[6] After alkylation of **7**, the resulting vinyl bromide was subjected to DIBAL-H reduction followed by acidic treatment to give rise to **9**. Compounds **11**, **12**, and **15** were synthesized by the same method described above.

After extensive investigation,[7] [Ni(tet a)]$(ClO_4)_2$ (5,5,7,-12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-nickel(II) perchlorate complex) was chosen as the catalyst for the present cyclization. Results of the cyclization are summarized in Table 1. First, the formation of the bicyclo-[2.2.0]heptane ring system was investigated. Electrolysis of *E*-olefin **5** provided *endo*-product **16** in 58% yield (entry 1). When the reaction was performed on *Z*-olefin **6**, *exo*-product **17** was obtained in 73% (entry 2).

Although there was question of stereoselectivity in the cyclization of **5**, the stereochemical outcome of electroreductive tandem cyclization of **6** could be rationalized as follows: the radical intermediate resulting from substrate **6** might react through either of the two conformers **A** and **B**. The allylic-type 1,3-strain interaction[8] in **B** between *pseudo* axial hydrogen and ester moiety causes the reaction to proceed predominantly via conformer **A** (Figure 1).

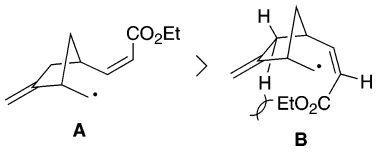


Figure 1. Conformations for electroreductive tandem cyclization.

Analyses of the $^1H-^1H$ COSY experiments of **16** and **17** enabled the assignment of all protons of each compounds. In addition, the relative stereochemistries were established on the basis of NOESY correlations as described in Figure 2.

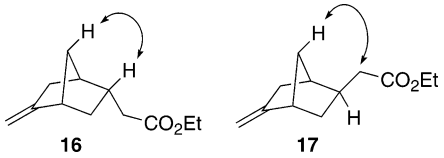


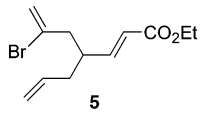
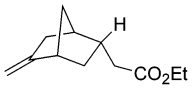
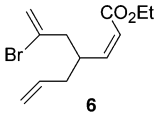
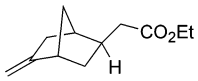
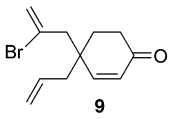
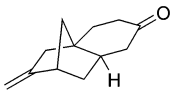
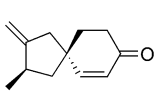
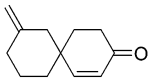
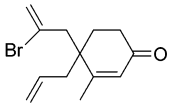
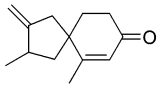
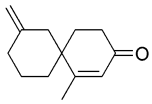
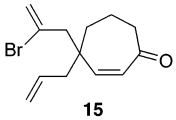
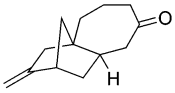
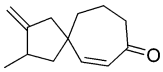
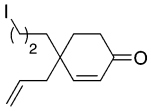
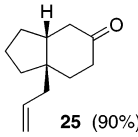
Figure 2. Significant NOESY correlations.

Encouraged by these results, we explored the construction of bridged tricyclic systems. The electroreductive tandem cyclization of 4-allyl-4-(2-bromoprop-2-en-1-yl)cyclohex-2-en-1-one (**9**) was conducted to lead to tricyclo[6.2.1.$0^{1,6}$]-undecan-4-one derivative **18**, in 50% yield, as well as spiro[4.5]decane **19** (3%) and spiro[5.5]undecane **20** (33%), produced through ring expansion.[9] The structures and relative stereochemistry of **18** and **19** were established by various spectral analyses.

When the reaction was run at 60 °C, it was complete in 20 h and gave **18** in 40% yield. By employing 20 mol % of

(4) Grimshaw, J. *Electrochemical Reactions and Mechanisms in Organic Chemistry*; Elsevier: Amsterdam, 2000.
(5) Ozaki, S.; Matsui, E.; Waku, J.; Ohmori, H. *Tetrahedron Lett.* **1997**, *38*, 2705.
(6) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(7) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677.
(8) For reviews, see: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375
(9) (a) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.

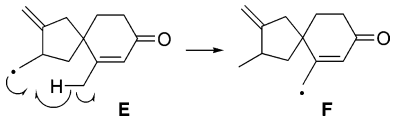
Table 1. Tandem Electroreductive Cyclization[a]

entry	substrate	time (h)	Product (yield)		
1	 **5**	14	 **16** (58%)		
2	 **6**	24	 **17** (73%)		
3	 **9**		 **18**	 **19**	 **20**
		48	50%	3%	33%
		20[b]	40%	7%	22%
		9[c]	50%	10%	27%
4	 **12**	48		 **21** (55%)[d]	 **22** (14%)[d]
5	 **15**	12[b]	 **23** (57%)	 **24** (19%)	
6	 **11**	1.5		 **25** (90%)	

[a] All reactions were carried out using $[Ni(tet\ a)](ClO_4)_2$ (10% mol) in DMF at rt. [b] 60 °C. [c] 60 °C, $[Ni(tet\ a)](ClO_4)_2$ (20% mol). [d] Based on recovered starting material.

$[Ni(tet\ a)](ClO_4)_2$ at 60 °C, the reaction was complete in 9 h and a 50% yield of **18** was isolated (entry 3). On the basis of this observation, the substituent effect on the enone moiety was next investigated. As a result, the reaction of **12** displayed completely different reactivity. Compound **12** did not provide any of the desired tricyclic compound, but instead a significant amount of **21** was generated along with **22** (entry 4). The formation of **21** is believed to proceed as outlined in Scheme 3. Homoallyl radical **E** arising from *5-exo-trig* cyclization undergoes 1,6-hydrogen atom transfer[10] to give the more stable radical **F**. As shown in entry 5, the present protocol is effective for the construction of tricyclo[7.2.1.0^{1,7}]-dodecane ring system **23** (57%). Interestingly, the reaction of iodide **11** afforded *cis*-hydrindan **25**, in 90% yield, in which *5-exo-trig* cyclization predominated.[11]

Scheme 3. 1,6-Hydrogen Transfer



In conclusion, tandem electroreductive cyclization has been successfully applied to the construction of tricyclo[6.2.1.0^{1,6}]-undecan-4-one and related polycyclic compounds. The favorable profile of this novel protocol is increased by the

(10) A recent review: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

(11) **Typical Procedure for Electroreduction.** Compound **6** (163 mg, 0.597 mmol), $[Ni(tet\ a)](ClO_4)_2$ (32 mg, 59.4 μmol), NH_4ClO_4 (141 mg, 1.20 mmol), and Et_4NClO_4 (35.4 mg, 0.154 mmol) were dissolved in 12 mL of dimethylformamide. This clear solution was transferred to one compartment of a separable H-type cell, divided by a Nafion 117 ion-exchange membrane. This compartment was then equipped with a graphite felt cathode and Ag/AgCl reference electrode. The electrolyte was degassed by bubbling nitrogen through it for 45 min. The platinum counter electrode was equipped with the other compartment and filled with 12 mL of dimethylformamide containing Et_4NClO_4 (35.4 mg, 0.154 mmol). Electroreduction was carried out potentiostatically at −1.32 V under nitrogen gas at room temperature. After 14 h, the reaction mixture was diluted with 30 mL of Et_2O and separated. The ethereal layer was washed three times with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel using 97:3 hexane/EtOAc to provide **17** (89 mg, 73%) as an oil.

low cost as well as the toxicologically and environmentally benign character of electrochemistry.

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Supporting Information Available: Experimental and spectral data along with ^{1}H and ^{13}C NMR spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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