Pergamon

Tetrahedron Letters 43 (2002) 2881–2884

TETRAHEDRON LETTERS

Electrochemical generation of tetraethylammonium *N*-acetoacetyloxazolidin-2-one enolates: an easy access to α-alkylated acetoacetic derivatives

Laura Palombi,[a,*] Marta Feroci,[b] Monica Orsini,[a] Leucio Rossi[a] and Achille Inesi[a,*]

[a]*Dip. di Chimica, Ingegneria Chimica e Materiali, Università degli Studi, I-67040 Monteluco di Roio, L'Aquila, Italy*
[b]*Dip. di Ingegneria Chimica, Materiali, Materie Prime e Metallurgia, Università 'La Sapienza', Via Castro Laurenziano 7, I-00161 Roma, Italy*

Received 19 February 2002; revised 5 March 2002; accepted 7 March 2002

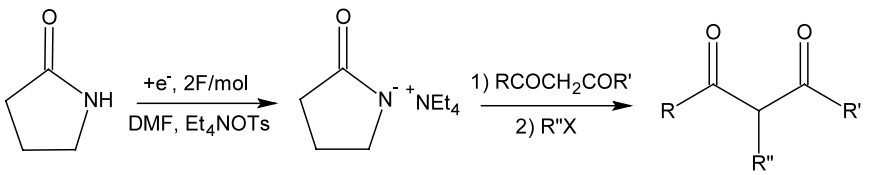
Abstract—A new electrochemical method for the mild generation of naked β-dicarbonyl derivative enolates is disclosed. The electrolysis, under galvanostatic control, of a solution of *N*-acetoacetyloxazolidin-2-ones/acetonitrile/tetraethylammonium perchlorate allowed the selective α-monoalkylation of the 1,3-dicarbonyl residue with a variety of alkyl halides, in very good yields and short reaction times. More interestingly, no by-products arising from either the electroreduction of the carbonyl functionalities or from nucleophilic cyanomethyl anion attack were detected. © 2002 Elsevier Science Ltd. All rights reserved.

In the field of the C–C bond-forming reactions, the α-alkylation of 1,3-dicarbonyl derivatives is one of the most used synthetic strategies. To this purpose, a considerable number of procedures have been reported in the literature, including the classical base-induced[1] and the metal-catalyzed alkylations.[2] The demand for such a variety of methods arises from the difficulty to have efficient, mild and selective procedures to circumvent the concurrent formation of side products (double alkylation, *O*-alkylation, β-diketone cleavage, etc.)[3] and, more recently, to also have low cost and environmentally safe methodologies.

In this regard, the exploitation of electrochemistry as a tool to generate bases and reactive species allowed us to set up new convenient procedures, with features of simplicity, cheapness and selectivity, very attractive from a synthetic standpoint.[4]

Shono and co-workers[5] for example, obtained very good results in the *C*-monoalkylation of 1,3-diketones and β-keto sulfones with alkyl halides by means of an electrogenerated base (2-pyrrolidone anion having tetraethylammonium as counterion) (Scheme 1). In that paper, the key role of tetraalkylammonium counterion as well as the advantage of the electroreductive method with respect to the chemical one were ascertained.

On the other hand, in our recent reports on the electrochemical-induced reactions of chiral nitrogen nucleophiles with acylating agents[6] and nitroalkenes,[7] we demonstrated the electrogeneration of *N*-anions by electrolysis under galvanostatic conditions in a system constituted by the substrate (chiral oxazolidin-2-one), the solvent (acetonitrile or propionitrile) and the supporting electrolyte (tetraethylammonium perchlorate (TEAP)). The addition of extra pro-bases was thus avoided.



Scheme 1.

* Corresponding authors. Tel.: +39-0862-434216; fax: +39-0862-434203; e-mail: palombi@ing.univaq.it; inesi@ing.univaq.it

PII: S0040-4039(02)00464-1

In connection with the above investigations, we tested the deprotonating ability of this electrochemical system on suitable methylene-active compounds.

In particular, it seemed intriguing to accomplish the electrogeneration of synthetically interesting *N*-acetoacetyloxazolidin-2-one enolates in order to examine their reactivity with alkyl halides. Especially, the expectation of a stereoselective C–C bond formation by using an optically active oxazolidin-2-one moiety as chiral inductor stimulated our interest.

It must be noted that, besides allowing access to various classes of enantiomerically pure α-alkylated acetoacetic derivatives by simple removal of the Evans' chiral auxiliary,[8] the α-adducts of compounds **1** are interesting as useful intermediates for the synthesis of enantiopure amino acids and substituted heterocyclic systems (such as oxazoles, isoxazoles and pyrazoles) incorporating the oxazolidin-2-one ring.[9]

In order to verify the efficiency of the electrochemical deprotonation an acetonitrile/TEAP[10] solution containing the model compound **1a**[11] was electrolysed at 0°C under galvanostatic control ($I=25$ mA cm^{-2}) in a divided cell equipped with a platinum cathode and anode. At the end of the electrolysis, the alkylating agent was added to the cathodic solution and the reaction was prolonged until TLC disappearance of the starting material (Scheme 2).

While the complete consumption of the starting material took 1.2 F per mol, we always observed a total chemoselectivity so that the α-adduct was the only product detectable by ^{1}H NMR analysis on the crude mixture.

As shown by the data reported in Table 1, the methodology could be generalized to the selective *C*-monoalkylation with various primary, benzylic and allylic halides. The reaction usually proceeded with high efficiency, as supported by ^{1}H NMR analysis on the crude products, while slightly lower yields were occasionally observed after standard purification procedures.

Since under the electrolysis conditions (CH_3CN/TEAP, galvanostatic control) two different reaction pathways could be proposed (direct cathodic cleavage of C–H bond[12] and indirect deprotonation of the methylene active compound by the electrogenerated base cyanomethyl anion which may form in the cathodic solution[13]), we have carried out a control experiment by adding the substrate **1a** to the pre-electrolysed solution of CH_3CN/TEAP (Scheme 3).

The following addition of BnBr led to the alkylation product with comparable yield selectivity and reaction time obtained herein before (i.e. Table 1, entry 6).

Although it has been reported that cyanomethyl anion adds to carbonyl compounds,[14] quite interesting, in our case, the cyanomethylation products arising from the attack to the β-dicarbonyl derivative was not obtained.

Finally, to check whether this electrochemical method enabled a stereoselective alkylation process, the investigation was extended to enantiomerically pure *N*-acetoacetyloxazolidin-2-ones **1b–f**.

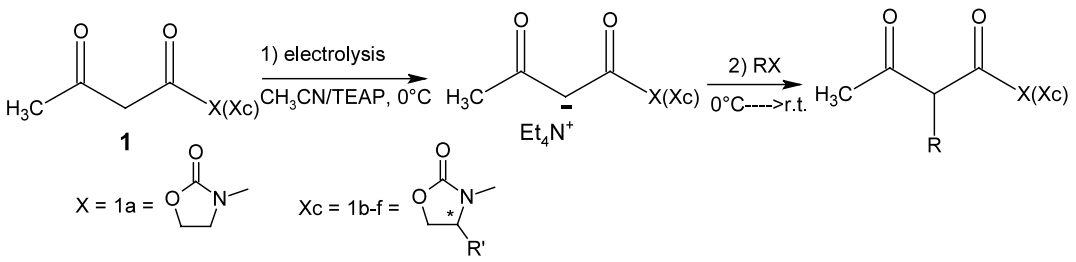
As reported in Table 2, alkylation reaction again took place with very satisfactory yields, affording a mixture of the two expected diastereoisomers. Although the diastereoisomeric ratios were generally low, noteworthy, the chiral oxazolidin-2-ones behaved like efficient resolving agents, allowing the access to both the enantiomerically pure epimers after silica gel chromatography.

In summary, we have demonstrated a new and mild electrochemical methodology to carry out the selective α-monoalkylation of *N*-acetoacetyl derivatives, avoiding either the use of chemical bases and probases or polluting metal reagents. Further investigations devoted to improve the stereoselectivity of the process are in progress.

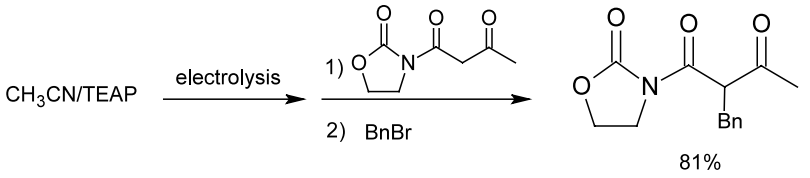
Table 1. Electrochemical activation and alkylation of *N*-acetoacetiloxazolidin-2-one **1a**

Entry	F (Mol)	RX	Time (h)	Yield[a] (%)
1	1.0	MeI	2	50
2	1.1	MeI	2	70
3	1.2	MeI	2	76
4	1.3	MeI	2	76
5	1.2	EtI	18	87 (>95)[b]
6	1.2	BnBr	2	83 (>95)[b]
8	1.2	H_2C=$CHCH_2Br$	4	82
9	1.2	CH_3CH=$CHCH_2Cl$	18	69

[a] Yields were calculated on the starting material and refer to isolated products.
[b] ^{1}H NMR yields.

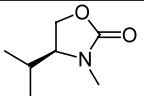
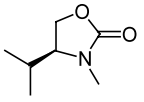
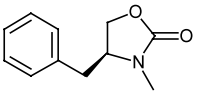
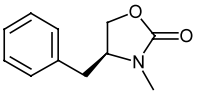
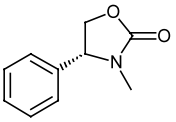
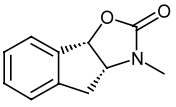
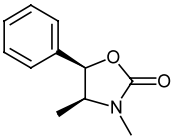


Scheme 2.



Scheme 3.

Table 2. Electrochemical activation and alkylation of *N*-acetoacetyloxazolidin-2-ones **1b–f**

Entry	F/mole	Xc	RX	Time (h)	Yield[a] (%)	d.r.
1	1.2	 (**1b**)	MeI	1	73	55:45
2	1.2	 (**1b**)	BnBr	1.5	92 (7)[b]	65:35
3	1.7	 (**1c**)	MeI	0.5	70 (6)[b]	57:43
4	1.2	 (**1c**)	BnBr	2	88 (>95)[c]	66:34
5	1.1	 (**1d**)	BnBr	2	80 (4)[b]	50:50
6	1.2	 (**1e**)	BnBr	2	75 (7)[b]	52:48
7	1.2	 (**1f**)	BnBr	2	87	64:36

[a] Yields were calculated on the starting material and refer to isolated products.
[b] Yields refer to the recovered unreacted starting material.
[c] ^{1}H-NMR yield.

Acknowledgements

The authors wish to thank Mr. Antonio Ficara for technical assistance and MURST (Cofin 2000) for financial support.

References

1. Smith, L. I.; Holum, J. R. *J. Am. Chem. Soc.* **1956**, *78*, 3417.
2. (a) Taylor, E. C.; Hawks, G. M., III; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421; (b) Bram, G.; Cabaret,

D.; Welvart, Z.; Geraghty, N. W. A.; Garvey, J. *Tetrahedron Lett*. **1988**, *29*, 4615–4618; (c) Moreno-Mañas, M.; Sebastian, R. M.; Vallribera, A.; Molins, E. *Tetrahedron* **1995**, *51*, 10795–10800.
3. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; pp. 492–546 and references cited therein.
4. Lund, H. In *Organic Electrochemistry*; Lund, H.; Hammerich, O., Eds.; Marcel Dekker: New York, 2001.
5. Shono, T.; Kashimura, S.; Sawamura, S.; Soejima, T. *J. Org. Chem*. **1988**, *53*, 907–910.
6. Feroci, M.; Inesi, A.; Palombi, L.; Sotgiu, G. *J. Org. Chem*. **2002**, *67*, 1719–1721.
7. Feroci, M.; Inesi, A.; Palombi, L.; Rossi, L. *Tetrahedron: Asymmetry* **2001**, *12*, 2331–2335.
8. For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 1.
9. (a) Galvez, N.; Moreno-Mañas, M.; Sebastian, R. M.; Vallribera, A. *Tetrahedron* **1996**, *52*, 1609–1616; (b) Lautens, M.; Roy, A. *Org. Lett*. **2000**, *2*, 555–557; (c) Moreno-Manas, M.; Sebastian, R. M.; Vallribera, A.; Carini, F. *Synthesis* **1999**, *1*, 157–161.
10. CAUTION: The use of perchlorates in an organic solvent must be considered as potentially dangerous. Take adequate precautions.
11. The substrates **1a–f** were prepared in a single step according to the procedure reported in the following references: (a) Hyatt, J. A.; Feldman, P. L.; Clemens, R. *J. Org. Chem*. **1984**, *49*, 5105; (b) Hyatt, J. A.; Clemens, R. *J. Org. Chem*. **1985**, *50*, 2431; (c) Clemens, R.; Witzeman, J. A. S. *J. Am. Chem. Soc*. **1989**, *111*, 2186.
12. Petrosyan, V. A. *Russ. Chem. Bull*. **1995**, *44*, 1411–1422.
13. Lund, H. *Organic Electrochemistry*; Lund, H.; Hammerich, O., Eds.; Marcel Dekker: New York, 2001; 264 and references cited therein.
14. Frink, B. T.; Hadad, C. M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2397–2407.