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Electrochemical generation of chiral oxazolidin-2-ones anions: a new procedure for the highly diastereoselective conjugate addition to nitroalkenes

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Abstract—A mild and efficient electrochemical alternative to classical base-catalyzed conjugate addition of nitrogen nucleophiles is reported here. The cleavage of the carbamic N–H bond of Evans' chiral auxiliaries can be very efficiently performed by electrolysis under galvanostatic control and the resulting naked anions used for highly diastereoselective conjugate addition to nitroalkenes. The degree of stereoselectivity was shown to depend on the steric hindrance of the group at the ring C(4) of the starting oxazolidin-2-one.

1. Introduction

The development of new and convenient strategies for stereoselective bond construction is an important objective in organic synthesis. In this field, optically active oxazolidin-2-one derivatives[1] attract wide interest because of their ability both as chiral auxiliaries and chiral synthons. Using oxazolidinones, many important goals have been achieved including the use of *N*-acyloxazolidinones in highly diastereoselective α-alkylations, conjugate additions, aldolic and metal-catalyzed pericyclic reactions.[2]

In contrast, with respect to the employment of oxazolidinones as sources of chiral nitrogen nucleophiles, few examples are reported in the literature.[3]

In spite of this, also established by Mioskowski et al. since 1997, the optically active addition products **2** of chiral oxazolidinones to nitroalkenes can be considered as versatile synthetic intermediates for the synthesis of biologically active compounds, providing access to non-naturally occurring α-amino acids,[4] vicinal diamines[5] and imidazolidinones[6] in enantiomerically enriched form.

The typical synthetic procedure for the generation of compounds of the type **2** involved the addition of the potassium salt of (*R*)- or (*S*)-4-phenyloxazolidin-2-one (generated by treatment of the oxazolidin-2-one with *tert*-BuOK) to monosubstituted nitroalkenes in the presence of 18-crown-6 to enhance the reactivity of the anion versus the addition (Fig. 1).

As part of our ongoing program devoted to the exploitation of electrochemical methodologies in organic synthesis,[7] we have already reported that the oxazolidinone N–H bonds may be efficiently cleaved during electrolysis under galvanostatic control of a solution of acetonitrile 0.1 M TEAP containing the oxazolidin-2-one, allowing the generation of their nitrogen anion.[8] We herein investigate the reactivity of these electrogenerated 'naked' anions as donors in conjugate additions with various nitroalkenes, as well as the efficiency and the stereochemical outcome of the reaction.

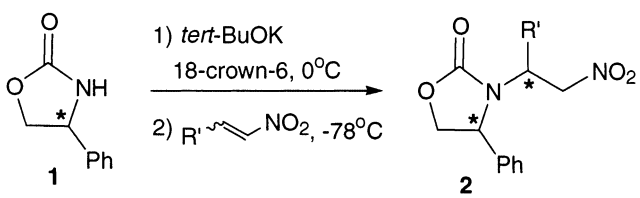

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Figure 1.

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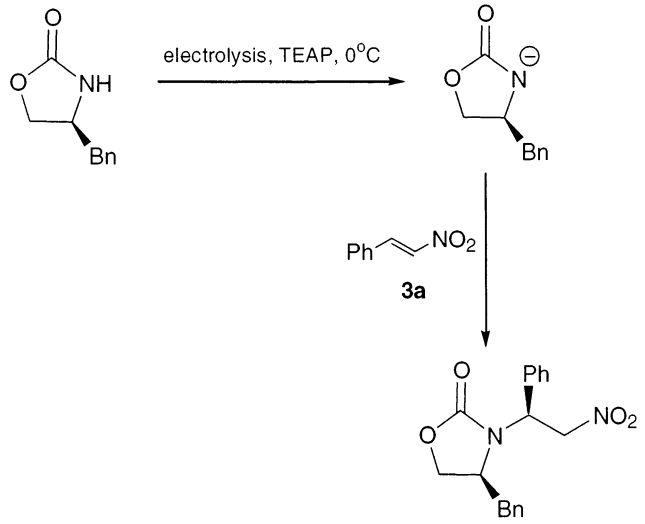
2. Results and discussion

In the preliminary screening, we probed the reactivity of the electrogenerated (*S*)-4-benzyloxazolidin-2-one anion in the reaction with commercially available β-nitrostyrene (Scheme 1); in order to optimize the experimental conditions, several experiments using various solvents, electrochemical conditions and temperatures were performed. The results are shown in Table 1.

It is noteworthy that the standard procedure used to perform electrochemical cleavage of the N–H bond does not involve the presence of any metallic counterion, and, as a consequence, the use of expensive crown ethers to increase the reaction rate is avoided.



Scheme 1.

As shown in Table 1, the reaction with β-nitrostyrene leads generally to moderate yields because of the marked tendency of the alkene to undergo polymerization. In fact, no nitroalkene was detected at the end of the reaction despite its employment in excess (see entry 4).

A remarkable improvement in the yield has been achieved by using a slight excess of the current quantity (1.4 F mol^{-1}), while higher diastereoisomeric excess was attained on performing the reactions at −78°C (in propionitrile) with no loss in efficiency or significant prolongation of the reaction time.

In order to generalize the procedure and, especially, to better understand the stereochemical outcome of the reaction, a series of enantiomerically pure oxazolidin-2-ones and nitroalkenes were tested under the optimized reaction conditions reported in Table 1, entry 5 (Scheme 2).

The results (Table 2) clearly show that the adducts **2** have been obtained in moderate to good yields, depending on the peculiar nitroalkene, with most of the oxazolidinones. Side products **4**, isolated as mixtures of diastereomers, were always observed in the reactions with the nitroalkene **3b**.

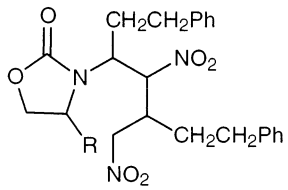


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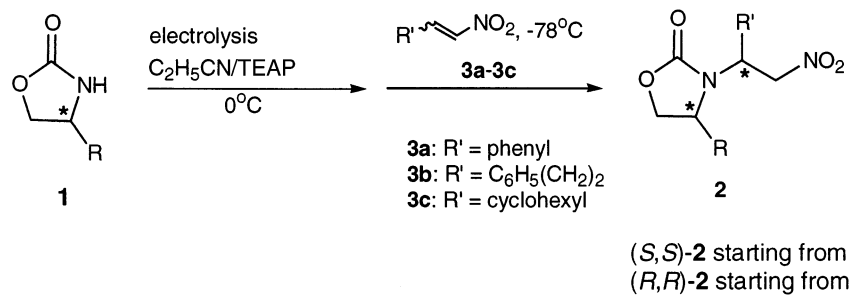
Table 1. Electrogeneration of (*S*)-4-benzyloxazolidin-2-one anion and conjugate addition to β-nitrostyrene

Entry	F/mol[a]	**3a**/**1a** ratio	Solvent	T^{b} (°C)	Yield (%)[c]	d.e. (%)[d]
1	1.1	2	CH_3CN	−20	34	74
2	1.4	2	CH_3CN	−20	43	76
3	2	2	CH_3CN	−45	34	85
4	1.4	4	CH_3CN	−45	37	85
5	1.4	2	C_2H_5CN	−78	42	90

[a] The number of Faradays is based on the moles of 4-benzyloxazolidin-2-one.
[b] Temperature values are those of the addition reactions.
[c] Yields were calculated based on the starting material and refer to isolated products.
[d] Evaluated by ^{13}C NMR spectroscopy.



Scheme 2.

Table 2. Conjugate addition of electrogenerated anions of compounds **1** with nitroalkenes **3a–c**

Entry	R	3[a]	*E*/*Z* ratio in 3[b]	3/1 ratio	Absolute configuration of **2**	Yield (%)[c]	d.e. (%)[d]	Yield and d.e.[e] (^{t}BuOK/crown ether system)
1	(*S*)-Phenyl-	**3a**	>99/1	2	(*S*,*S*)[f]	51	>98	54% (>98%)[g]
2	(*R*)-Phenyl-	**3a**	>99/1	2	(*R*,*R*)[f]	30	>98	43% (>98%)[g]
3	(*S*)-Phenyl-	**3b**	>99/1	1.1	(*S*,*S*)[h]	56	>98	
4	(*S*)-Benzyl-	**3b**	>99/1	1.1	(*S*,*S*)[h]	58	90 (>98%)[i]	
5	(*S*)-*iso*-Propyl-	**3b**	>99/1	1.1	(*S*,*S*)[h]	60	92 (>98%)[i]	
6	(*S*)-Benzyl-	**3c**	85/15	1.1	(*S*,*S*)[h]	65	90	
7	(*S*)-*iso*-Propyl-	**3c**	85/15	1.1	(*S*,*S*)[h]	76	92	
8	(*S*)-Phenyl-	**3c**	85/15	1.1	(*S*,*S*)[f]	88	>98	85% (>98%)
9	(*R*)-Phenyl-	**3c**	85/15	1.1	(*R*,*R*)[f]	79	>98	78% (>98%)
10	(*S*)-*tert*-Butyl-	**3c**	85/15	1.1	(*S*,*S*)[h]	79	>98	

[a] **3a** is a commercially available compound. **3b** and **3c** have been prepared according to Ref. 9.
[b] *E*/*Z* ratio of **3b** and **3c** was determined by ^{1}H and ^{13}C NMR.
[c] Yields refer to isolated products.
[d] Evaluated by ^{13}C NMR on the crude adducts **2**.
[e] The values of the diastereoisomeric ratio are reported in parentheses.
[f] Absolute configurations at the newly created stereogenic center have been established by comparison of the optical rotations with the ones reported in the literature (Ref. 3).
[g] In these cases a five-fold excess of β-nitrostyrene was employed.
[h] In these cases we assume that the diastereofacial selection occurred in the same way as for the entries 1, 2, 8 and 9.
[i] Values in parentheses refer to the diastereoisomeric ratios obtained for the products after recrystallization.

Concerning the stereochemical aspects of the reaction, we found (in complete agreement with the previously published observation of Mioskowski), that the diastereoselectivity of our procedure was not dependant on the geometry of the nitroalkene double bond. Therefore, the addition products could be achieved as a single adducts even if an *E*/*Z* mixture of (2-nitrovinyl)cyclohexane was used (Table 2, entries 8–10).

In contrast, the results obtained show that the chiral induction was controlled by the absolute configuration of the stereogenic center at C(4) of the oxazolidin-2-ones and that the diastereomeric excess of the product was strongly dependent on the steric hindrance effects from the R group present. So that, while the bulky substituents phenyl and *t*-butyl always imply complete diastereoselectivity with all nitroalkenes used, lower diastereomeric excesses have been observed with oxazolidin-2-ones bearing less sterically demanding benzyl and isopropyl groups.

3. Conclusions

In conclusion, exploiting electrochemical methodology, we have demonstrated a new and mild procedure for the synthesis of compounds of the type **2**, well-known key-intermediates in the synthesis of a variety of biologically active compounds.

Furthermore, as regards the stereochemical aspects of this reaction, the results reported here represent the first data showing the critical influence of the R group in position 4 of the oxazolidin-2-one ring on the observed diastereoselectivity.

4. Experimental

4.1. General

The electrochemical apparatus and the cells, NMR and polarimeter instruments are described elsewhere.[10]

Dry acetonitrile (Lab-scan, anhydroscan) was used as received, while propionitrile was freshly distilled twice from CaH_2. Tetraethylammonium perchlorate (TEAP) was purified as already described.[11] Flash chromatography was performed with silica gel (230–400 mesh Merck). TLC analysis was carried out on Merck Kieselgel F_{254} plates. I_2 and UV light were used as detector systems.

4.2. Electrolyses and conjugate addition to nitroalkenes. General procedure

A solution of oxazolidin-2-one (1 mmol) in anhydrous propionitrile (20 mL of 0.1 M propionitrile solution of TEAP) was electrolysed at 0°C, under galvanostatic control (I=25 mA cm^{-2}) in a divided cell (platinum gauze cathode and anode). At the end of the electrolysis the cathodic solution was transferred, under an Argon atmosphere, in a flask and cooled at −78°C. A solution of nitroalkene in propionitrile (3 mL), previously cooled at −78°C, was then added dropwise via cannula. TLC analysis showed the rapid disappearance of the nitroalkene. The reaction was quenched with saturated aqueous NH_4Cl, and the organic phase was extracted twice with diethyl ether. The combined organic phases were then washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography eluting with a mixture of petroleum ether/ethyl acetate.

4.3. Isolated products

The addition products reported in Table 2 (entries 1, 2, 8 and 9) gave spectral data and optical rotations according to the literature.[3]

4.3.1. (4*S*)-Benzyl-3-(2-nitro-1-phenylethyl)oxazolidin-2-one. Table 1: inseparable mixture of epimers as a colorless solid. Spectroscopic data for the major (*S*,*S*)-diastereoisomer: ^{1}H NMR ($CDCl_3$) $\delta=7.50$–7.00 (m, 10H); 5.76 (dd, 1H, $J_1=12.5$ Hz, $J_2=7.5$ Hz); 5.01 (dd, 1H, $J_1=12.5$ Hz, $J_2=5.0$ Hz); 4.76 (dd, 1H, $J_1=7.5$ Hz, $J_2=5.0$ Hz); 4.15–3.75 (m, 3H); 3.10 (dd, 1H, $J_1=12.5$ Hz, $J_2=3.75$ Hz); 2.60 (dd, 1H, $J_1=12.5$ Hz, $J_2=7.5$ Hz). ^{13}C NMR ($CDCl_3$) $\delta=158.07$; 135.54; 135.01; 129.63–127.59 (six peaks); 75.64; 67.75; 56.78; 56.26; 39.72. Anal. calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58; O, 19.61. Found: C, 66.35; H, 5.60; N, 8.65; O, 19.40%.

4.3.2. (4*S*)-Phenyl-3-((*S*)-1′-(nitromethyl)propyl-3′-phenyl)oxazolidin-2-one. Table 2, entry 3: colorless solid. $[\alpha]_D=+62.8$ ($c=0.70$, $CHCl_3$). ^{1}H NMR ($CDCl_3$) $\delta=7.50$–6.90 (m, 10H); 4.83 (dd, 1H, $J_1=14.0$ Hz, $J_2=8.0$ Hz); 4.63–4.43 (m, 3H); 4.19 (dd, 1H, $J_1=6.0$ Hz, $J_2=2.0$ Hz); 3.93–3.79 (m, 1H); 2.71–2.63 (m, 2H); 2.12 (ept, 1H $J=8.0$ Hz) 1.87 (ept, 1H $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) $\delta=157.25$; 139.80; 137.10; 129.71–126.52 (six peaks); 75.78; 70.19; 60.90; 52.50; 32.30; 30.89. Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; O, 18.80. Found C, 67.15; H, 6.00; N, 8.40; O, 18.46%.

4.3.3. (*S*)-4-Benzyl-3-((*S*)-1′-(nitromethyl)propyl-3′-phenyl)oxazolidin-2-one. Table 2, entry 4: purification by chromatography afforded crude product as a 95:5 mixture of epimers. The major (*S*,*S*)-epimer was isolated after two recrystallizations (pentane/EtOAc) as colorless needles: $[\alpha]_D=+29.7$ ($c=0.875$, $CHCl_3$). ^{1}H NMR: ($CDCl_3$) $\delta=7.50$–6.90 (m, 10H); 5.12 (dd, 1H, $J_1=14.0$ Hz, $J_2=9.2$ Hz); 4.49 (dd, 1H, $J_1=14.0$ Hz, $J_2=4.6$ Hz); 4.20–3.60 (m, 4H); 2.88 (dd, 1H, $J_1=12.0$ Hz, $J_2=4.0$ Hz); 2.63 (t, 2H, $J=7.4$ Hz); 2.45–2.15 (m, 2H); 2.05 (m, 1H). ^{13}C NMR ($CDCl_3$) $\delta=157.10$; 139.62; 134.85; 128.98–126.66 (six peaks); 76.06; 67.62; 57.96; 52.44; 38.97; 32.25; 30.60. Anal. calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90; O, 18.06. Found: C, 67.70; H, 6.29; N, 7.93; O, 18.08%.

4.3.4. (4*S*)-*iso*-Propyl-3-((*S*)-1′-(nitromethyl)propyl-3′-phenyl)oxazolidin-2-one. Table 2, entry 5: purification by chromatography afforded the crude product as a 96:4 mixture of epimers. The major (*S*,*S*)-epimer was isolated after two recrystallizations (pentane/EtOAc) as colorless needles: $[\alpha]_D=+45.7$ ($c=0.70$, $CHCl_3$). ^{1}H NMR: ($CDCl_3$) $\delta=7.35$–7.00 (m, 5H); 5.04 (dd, 1H, $J_1=12.8$ Hz, $J_2=8.0$ Hz); 4.58 (dd, 1H, $J_1=12.8$ Hz, $J_2=5.5$ Hz); 4.10–3.80 (m, 4H); 3.50–2.90 (m, 1H); 2.67 (t, 2H, $J=7.6$ Hz); 2.27 (ept, 1H, $J=7.6$ Hz); 1.98 (ept., 1H, $J=7.6$ Hz); 0.76 (d, 3H, $J=3.0$ Hz); 0.73 (d, 3H, $J=2.7$ Hz). ^{13}C NMR ($CDCl_3$) $\delta=157.60$; 139.73; 128.71; 128.09; 126.54; 63.17; 61.59; 52.92; 33.45; 31.28; 28.68; 18.12; 14.11. Anal. calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14; O, 20.89. Found: C, 62.75; H, 7.25; N, 9.10; O, 20.91%.

4.4. (4*S*)-Benzyl-3-(1′-cyclohexyl-2′-nitroethyl)-oxazolidin-2-one

Table 2, entry 6: inseparable mixture of epimers as a colorless solid. Spectroscopic data for the major (*S*,*S*)-diastereoisomer: ^{1}H NMR ($CDCl_3$) $\delta=7.30$–7.00 (m, 5H); 5.19 (dd, 1H, $J_1=12.5$ Hz, $J_2=10.0$ Hz); 4.09 (dd, 1H, $J_1=12.5$ Hz, $J_2=5.0$ Hz); 4.10–3.30 (m, 3H); 3.62 (dt, 1H, $J_1=17.5$ Hz, $J_2=5.0$ Hz); 3.0 (dd, 1H, $J_1=12.5$ Hz, $J_2=2.5$ Hz); 2.87 (dd, 1H, $J_1=12.5$ Hz, $J_2=10.0$ Hz); 2.10–1.95 (m, 1H); 1.95–1.50 (m, 4H); 1.40–0.70 (m, 6H). ^{13}C NMR ($CDCl_3$) $\delta=156.98$; 134.97; 128.86; 128.83; 127.13; 76.40; 67.37; 59.05; 58.50; 38.54; 38.21; 30.37; 29.95; 25.46. Anal. calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43; O, 19.25. Found: C, 65.10; H, 7.38; N, 8.90; O, 18.63%.

4.5. (4*S*)-*iso*-Propyl-3-(1′-cyclohexyl-2′-nitroethyl)-oxazolidin-2-one

Table 2, entry 7: inseparable mixture of epimers as a colorless solid. Spectroscopic data for the major (*S*,*S*)-diastereoisomer: ^{1}H NMR ($CDCl_3$) $\delta=5.20$ (dd, 1H, $J_1=14.0$ Hz, $J_2=8.4$ Hz); 4.6 (dd, 1H, $J_1=14.0$ Hz, $J_2=4.0$ Hz); 4.22 (t, 1H, $J=10.0$ Hz); 4.05 (dd, 1H, $J_1=8.4$ Hz, $J_2=4.2$ Hz); 3.63–3.53 (m, 2H); 2.10–1.45 (m, 8H); 1.25–0.55 (m, 10H). ^{13}C NMR ($CDCl_3$) $\delta=$ 157.50; 75.38; 62.72; 62.66; 58.47; 38.69; 30.01; 29.70; 28.45; 25.59; 25.44; 25.41; 18.11; 13.74. Anal. calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85; O, 22.51. Found: C, 59.22; H, 8.47; N, 9.92; O, 22.39%.

4.6. (4*S*)-*tert*-Butyl-3-((*S*)-1′-cyclohexyl-2′-nitroethyl)-oxazolidin-2-one

Table 2, entry 10: colorless solid. $[\alpha]_D=+52.6$ ($c=0.57$, $CHCl_3$). ^{1}H NMR ($CDCl_3$) $\delta=5.10$–4.89 (m, 2H); 4.42–4.12 (m, 2H); 3.90–3.70 (m, 1H); 3.42 (dd, 1H, $J_1=10$ Hz, $J_2=3.3$ Hz); 2.21–1.90 (m, 1H); 1.74–1.55 (m, 6H); 1.26–0.95 (m, 13H). ^{13}C NMR ($CDCl_3$) $\delta=158.61$; 77.95; 67.90; 65.34; 59.87; 40.56; 35.05; 30.19; 29.55; 25.79; 25.70; 25.63; 25.56. Anal. calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39; O, 21.45. Found: C, 60.42; H, 8.70; N, 9.37; O, 21.51%.

Acknowledgements

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