

VERSATILE ROUTES TO CHIRAL 4-SUBSTITUTED 2-OXAZOLIDINONES AND α -AMINO ACIDS. USE OF CHIRON, [4+2] CYCLOADDUCTS OF DIALKYL AZODICARBOXYLATES AND 2-OXAZOLONES

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The thermal reaction of 3-[(1*S*)-2-alkoxy-1-apocamphanecarbonyl]-2-oxazolones with dialkyl azodicarboxylates results in exclusive formation of [4+2] type cycloadducts with moderate levels of diastereofacial selection, which serve as versatile chiral synthons for a wide variety of 4-alkyl and 4-aryl-2-oxazolidinones as well as α -amino acids.

KEYWORDS 2-oxazolone; azodicarboxylate; [4+2] cycloaddition; deacylation; chiral synthon; organocuprate; 2-aminoalcohol; 2-oxazolidinone; α -amino acid

We previously developed a promising methodology to utilize a simple heterocycle, 2-oxazolone (1), as a building block for β -aminoalcohols of biological interest, in which highly regio- and diastereoselective electrophilic additions at the 4,5-olefinic moiety were involved as key steps.¹⁾ On the other hand, the 4,5-unsubstituted 2-oxazolones were reported to act as good dienophiles in thermal [4+2] cycloaddition reactions only when reactive dienes such as cyclopentadiene and benzofuran were employed under forcing conditions of prolonged heating at elevated temperature.^{2,3)}

We have now found that the thermal cycloadditions of 2-oxazolones (1) to dialkyl azodicarboxylates (2) smoothly proceed under quite mild conditions (at 80 °C) to give excellent yields of the regioselectively controlled [4+2] cycloadducts (3). None of the other plausible addition products, such as diazetidines (4) (1,2-addition) and isoxazolidines (5) (1,3-addition), was spectroscopically detectable (Chart 1).⁴⁾

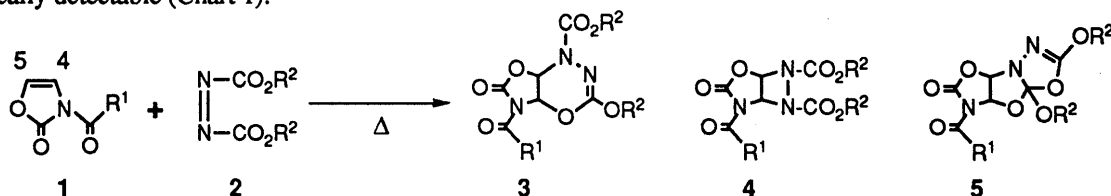


Chart 1

Thus, 3-[(1*S*)-2-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (6) were treated with a series of azodicarboxylates in boiling benzene for 6 ~19 h to give excellent yields of the diastereomeric mixture of 7 and 8, which were readily separable by chromatography on silica gel, with moderate diastereoselectivity (TABLE I). The use of bulky R² and R³ groups in the reactants improved the diastereoselectivity to as much as 72% d.e., and the highly congested 2-neopentyloxy-1-apocamphanecarboxylic acid appears to be the chiral auxiliary of choice in the present cycloadditions.

The structures of the isomeric cycloadducts thus formed were elucidated as 1,4-cycloaddition products on the basis of the spectral data (¹H- and ¹³C-NMR, IR, MS). In view of the variety of conceivable addition modes, X-ray crystallographic analysis of the key adduct 7 (R²=R³=Me) was performed, providing unequivocal proof of the [4+2] addition structure (Fig. 1).⁵⁾

The optically pure cycloadducts were rapidly cleaved in quantitative yields with a catalytic amount of *p*-toluenesulfonic acid in methanol to form *trans*-4-methoxy oxazolidinones, as illustrated by the facile conversion of 9 to 10. Though removal of the sterically congested *N*-acyl group from 10 was difficult even

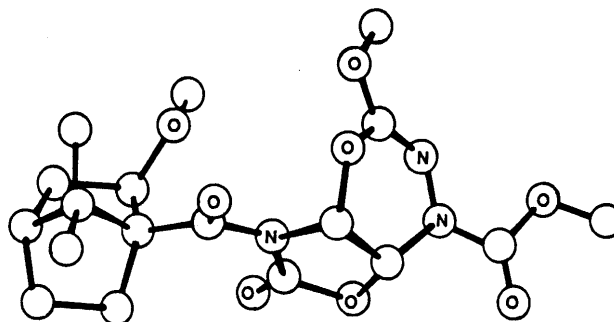


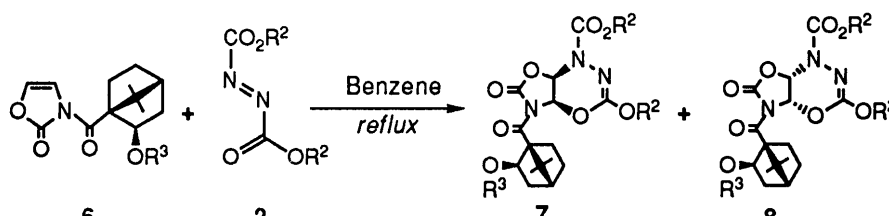
Fig.1. Perspective View of the Cycloadduct (7)
(R²=R³=Me)

with reagents such as lithium benzylmercaptide⁶⁾ and hydroperoxide,⁷⁾ due to the low reactivity and the accompanying endocyclic cleavage,⁸⁾ the reductive system derived from LiBH₄ and methanol (1:2) was found to be exceptionally effective at 0 °C and compound **10** was readily deacylated to *trans*-4-methoxy-5-hydrazino-2-oxazolidinone (**11**) in satisfactory yield (above 70%) with recovery of the reduced auxiliary.⁹⁾

The following conversions to 2-aminoalcohol derivatives (**14**) prove the synthetic versatility as chiral synthons (Chart 2). On treatment with organocuprates/BF₃OEt₂, the 4-methoxy derivative (**11**) underwent smooth replacement of the methoxy group with a wide variety of *prim.* to *tert.*-alkyls and aryls with full retention of configurations to give the *trans*-derivatives **12** exclusively (TABLE II). No *cis*-isomer could be detected in the NMR spectra (400 MHz). Subsequent protection of the NH-groups of **12** with Boc followed by reductive ring cleavage gave high to excellent yields (above 77%) of (*R*)-*N*-Boc-2-aminoalcohols (**14**), which serve as versatile intermediates. Thus, treatment with thionyl chloride resulted in exclusive formation of (*R*)-4-substituted 2-oxazolidinones (**15**), which worked as Evans' auxiliaries (TABLE III). Oxidation with pyridinium dichromate (PDC)¹⁰⁾ gave unnatural type α -amino acids such as (*R*)-*tert*-leucine (**16**, R⁴=*t*-Bu) and (*R*)-valine (**16**, R⁴=*i*-Pr) in 83% and 87% yields, respectively.

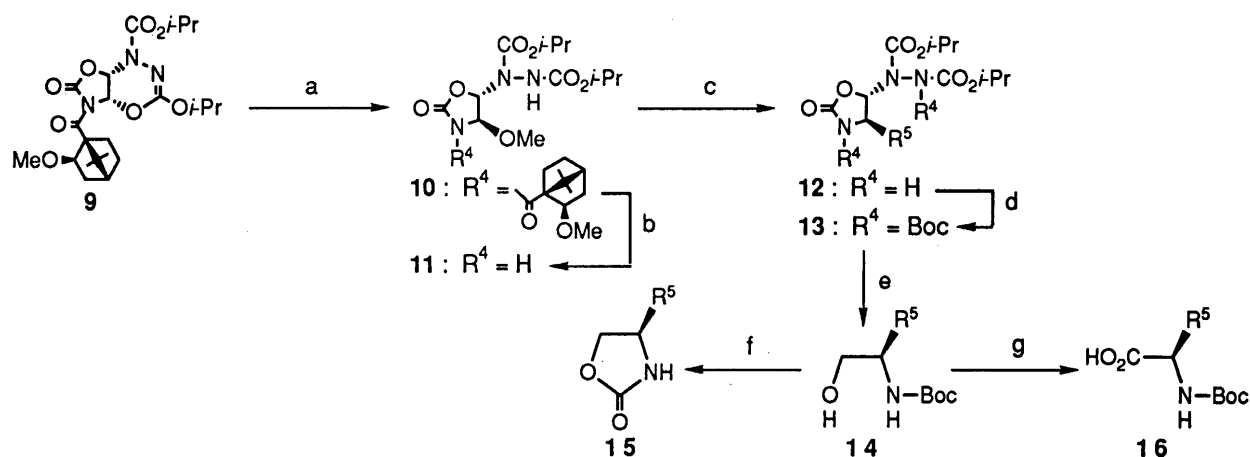
In conclusion, 3-acyl-2-oxazolones undergo smooth cycloaddition with dialkyl azodicarboxylates under mild conditions to give [4+2] cycloadducts, which serve as versatile synthons for a wide variety of optically active 4-substituted 2-oxazolidinones and α -amino acids.

TABLE I. Diastereoselective [4+2] Cycloaddition of Azodicarboxylates(2) to 2-Oxazolones(6)



Entry	R ³	R ²	Time (h)	Yield (%) ^{a)}	7 : 8 ^{b)}	(%d.e.)
1	Me	<i>i</i> -Pr	12	93	24 : 76	(52)
2	Pr	Bzl	6	86	18 : 82	(64)
3	CH ₂ CM ₃	Me	12	83	16 : 84	(68)
4	CH ₂ CM ₃	<i>i</i> -Pr	19	85	15 : 85	(70)
5	CH ₂ CM ₃	Bzl	18	93	14 : 86	(72)

a) Isolated yields. b) Determined from ¹H-NMR (400 MHz) spectral data.



a) *p*-TosOH (0.05 eq.), MeOH; r.t., 5 min. b) LiBH₄ (4 eq.), MeOH (8 eq.), THF; 0 °C, 2.5h c) See Table 2. d) (Boc)₂O, NEt₃, DMAP, CH₂Cl₂; r.t., 4h e) NaBH₄ (4 eq.), MeOH (4 eq.), EtOH; r.t., 24h f) SOCl₂ (8 eq.), THF; r.t., 3h g) PDC, DMF; r.t.

Chart 2

TABLE II. The BF_3 -Promoted Substitution of 4-Methoxy-2-oxazolidinone (11) by Organocuprates

Entry	Reagents	Product 12, R^5	Yield (%) ^{a)}
1	<i>i</i> -PrCuCNMgBr (4 eq.), LiCl (8.8 eq.)	<i>i</i> -Pr	85 (100)
2	(<i>t</i> -Bu) ₂ CuCN(MgBr) ₂ (4 eq.)	<i>t</i> -Bu	75 (87)
3	PhCuCNMgBr (4 eq.), LiCl (8.8 eq.)	Ph	85 (99)
4	(PhCH ₂) ₂ CuCN(MgCl) ₂ (4 eq.)	Bzl	79 (92)

a) Yields and *trans* stereochemistry were determined from $^1\text{H-NMR}$ (400 MHz) analysis. The values in parentheses are corrected yields based on unrecovered 11.

TABLE III. Conversion of *N*-Boc-2-Aminoalcohols (14) to (*R*)-4-Substituted 2-oxazolidinones (15)^{a)}

R^5	<i>i</i> -Pr	<i>t</i> -Bu	Ph	CH_2Ph
Yield (%)	100	100	100	97

a) The aminoalcohol (14) was treated with SOCl_2 in THF at room temperature for 3h.

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- 5) Crystal data for compound 7 ($\text{R}^2=\text{R}^3=\text{Me}$) [mp 195.3~196.0 °C, $[\alpha]_{\text{D}}^{26}$ -279.7° (c. 0.97, CHCl_3)] : orthorhombic, $\text{P}2_12_12_1$, $a=12.258(1)$, $b=18.482(2)$, $c=9.009(1)\text{\AA}$. The structure was refined to an R-value of 5.3%.
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- 8) Exocyclic deacylation of 10 to 11 by the conventional reagents resulted in only poor yields as follows.

Entry	Reagent	Conditions	Yield (%) ^{a)}
1	Bu_2CuLi (8 eq.)	THF; -30 °C to 0 °C	16 (14)
2	LiOH (5 eq.)	$\text{MeOH-H}_2\text{O}(5:1)$; r.t., 3h	0
3	PhCH_2OLi (2 eq.)	THF; -78 °C to r.t.	11
4	PhCH_2SLi (1.5 eq.)	THF; 0 °C, 2h	23
5	LiOOH (2 eq.)	$\text{THF-H}_2\text{O}(4:1)$; 0 °C to r.t.	23 (44)
6	LiBH_4 (4 eq.)	THF; 0 °C to r.t.	21

a) Isolated yields. The values in parentheses are recovery yields.

- 9) The amount of methanol is critical in the selective exocyclic deacylation and the $\text{LiBH}_4:\text{MeOH}$ ratio of 1 to 2 was optimal under the conditions employed. Reactions of 10 with the reagents $\text{LiBH}_4/\text{MeOH}$ in the ratios of 1:1 and 1:3 gave the 2-oxazolidinone (11) in 57% and 40% yields, respectively.
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(Received February 6, 1992)