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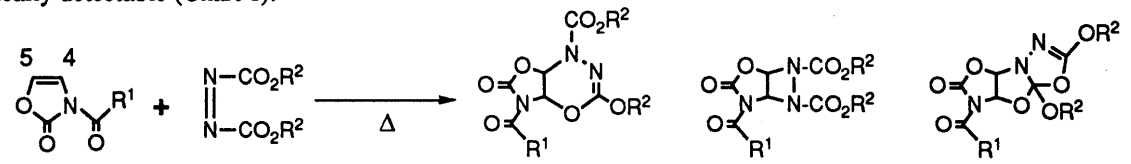
The thermal reaction of 3-[(*1S*)-2-alkoxy-1-apocamphanecarbonyl]-2-oxazolones with dialkyl azodicarboxylates results in exclusive formation of [4+2] type cycloadducts with moderate levels of diastereofacial selection, which serve as versatile chiral synthons for a wide variety of 4-alkyl and 4-aryl-2-oxazolidinones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



1 **2** **3** **4** **5**

Chart 1

Thus, 3-[(*1S*)-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 R^2 and R^3 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 (^{1}H- and ^{13}C-NMR, IR, MS). In view of the variety of conceivable addition modes, X-ray crystallographic analysis of the key adduct **7** (R^2=R^3=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

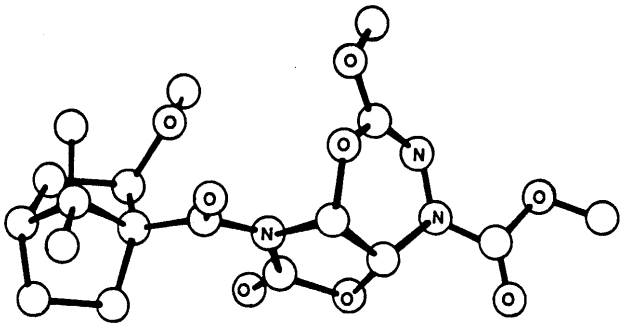


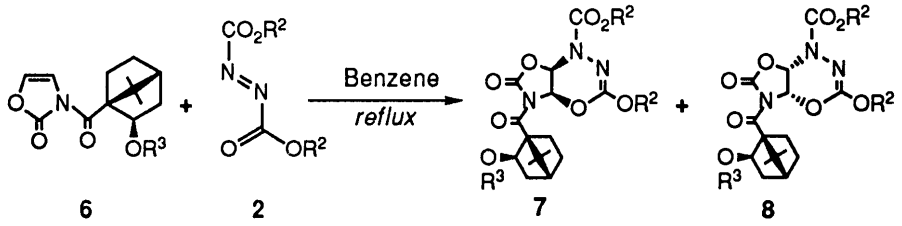
Fig.1. Perspective View of the Cycloadduct (7) (R^2=R^3=Me)

with reagents such as lithium benzylmercaptide[6] and hydroperoxide,[7] due to the low reactivity and the accompanying endocyclic cleavage,[8] the reductive system derived from $LiBH_4$ 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/BF_3OEt_2, 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**, R^4=*t*-Bu) and (*R*)-valine (**16**, R^4=*i*-Pr) in 83% and 87% yields, respectively.

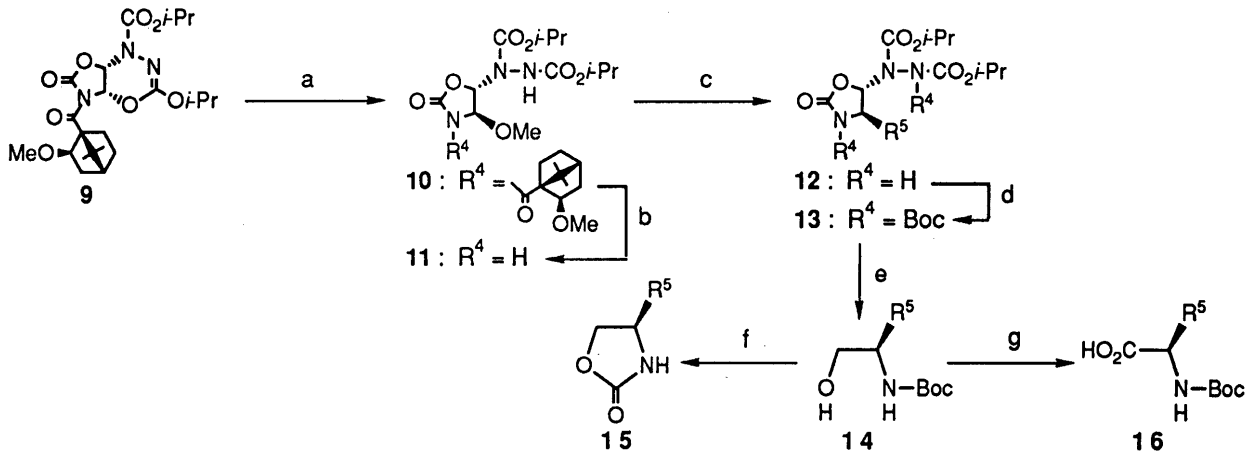
In conclusion, 3-acyl-2-oxazolones undergo smooth cycloaddition with dialkyl azodicarboxylates under mild conditions to give [4+2] cycloadducts, which serve as versatile synthons for a wide variety of optically active 4-substituted 2-oxazolidinones and α-amino acids.

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*-Pr	12	93	24 : 76	(52)
2	Pr	Bzl	6	86	18 : 82	(64)
3	CH_2CMe_3	Me	12	83	16 : 84	(68)
4	CH_2CMe_3	*i*-Pr	19	85	15 : 85	(70)
5	CH_2CMe_3	Bzl	18	93	14 : 86	(72)

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



a) *p*-TosOH (0.05 eq.), MeOH; r.t., 5 min. b) $LiBH_4$ (4 eq.), MeOH (8 eq.), THF; 0 °C, 2.5h c) See Table 2. d) $(Boc)_2O$, NEt_3, DMAP,CH_2Cl_2; r.t., 4h e) $NaBH_4$ (4 eq.), MeOH (4 eq.), EtOH; r.t., 24h f) $SOCl_2$ (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*-PrCuCNMgBr (4 eq.), LiCl (8.8 eq.)	*i*-Pr	85 (100)
2	$(t\text{-Bu})_2CuCN(MgBr)_2$ (4 eq.)	*t*-Bu	75 (87)
3	PhCuCNMgBr (4 eq.), LiCl (8.8 eq.)	Ph	85 (99)
4	$(PhCH_2)_2CuCN(MgCl)_2$ (4 eq.)	Bzl	79 (92)

a) Yields and *trans* stereochemistry were determined from ^{1}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*-Pr	*t*-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.

REFERENCES AND NOTES

1) a) T. Kunieda, T. Ishizuka, T. Higuchi and M. Hirobe, *J. Org. Chem.*, **53**, 3381 (1988); b) T. Ishizuka, S. Ishibuchi and T. Kunieda, *ibid.*, **30**, 3449 (1989); c) S. Ishibuchi, Y. Ikematsu, T. Ishizuka and T. Kunieda, *Tetrahedron Lett.*, **32**, 3523 (1991); d) T. Ishizuka and T. Kunieda, *J. Synth. Org. Chem., Jpn.*, **49**, 118 (1991).

2) K. -H. Scholz, H. -G. Heine and W. Hartmann, *Justus Liebigs Ann. Chem.*, **1977**, 2027.

3) J. A. Deyrup and H. L. Gingrich, *Tetrahedron Lett.*, **1977**, 3115.

4) a) J. Firl and S. Sommer, *Tetrahedron Lett.*, **1972**, 4713; b) J. Firl and S. Sommer, *ibid.*, **1971**, 4193; c) E. K. von Gustorf, D. V. White, B. Kim, D. Hess and J. Leitich, *J. Org. Chem.*, **35**, 1155 (1970); d) J. Firl and S. Sommer, *Tetrahedron Lett.*, **1970**, 1929; e) J. Firl and S. Sommer, *ibid.*, **1970**, 1925; f) E. K. von Gustorf, D. V. White, J. Leitich and D. Hanneberg, *ibid.*, **1969**, 3113; g) E. K. von Gustorf, D. V. White and J. Leitich, *ibid.*, **1969**, 3109; h) J. Firl and S. Sommer, *ibid.*, **1969**, 1137; i) J. Firl and S. Sommer, *ibid.*, **1969**, 1133.

5) Crystal data for compound **7** (R^2=R^3=Me) [mp 195.3~196.0 °C, $[\alpha]_D^{26}$ -279.7° (c. 0.97, $CHCl_3$)] : orthorhombic, P212121, a=12.258(1), b=18.482(2), c=9.009(1)Å. The structure was refined to an R-value of 5.3%.

6) R. E. Damon and G. M. Coppola, *Tetrahedron Lett.*, **31**, 2849 (1990).

7) D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.*, **28**, 6141 (1987).

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.)	MeOH-H_2O(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.)	THF-H_2O(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 $LiBH_4$:MeOH ratio of 1 to 2 was optimal under the conditions employed. Reactions of **10** with the reagents $LiBH_4$/MeOH in the ratios of 1:1 and 1:3 gave the 2-oxazolidinone (**11**) in 57% and 40% yields, respectively.

10) N. A. Sasaki, C. Hashimoto and P. Potier, *Tetrahedron Lett.*, **28**, 6069 (1987).

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