Nucleophilic Ring Opening of 3-Benzyl-1,3-oxazinanes by Reformatsky Reagents. A Synthesis of β-Amino Ester Derivatives

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2-Substituted 3-benzyl-1,3-oxazinanes react with the Reformatsky reagent derived from ethyl 2-bromoacetate and zinc, using very mild conditions (0°C, 1 h) leading regioselectively to 3-substituted ethyl 3-[(3-hydroxypropyl)benzylamino]propanoates in high yield.

The synthesis of β-amino acid derivatives has been extensively studied due to their biological interest and their use as starting materials in the preparation of β-lactams.[1] The most general methods are: 1,4-addition of nitrogen derivatives to α,β-unsaturated nitriles, esters or acids followed by hydrolysis, the homologation of α-amino acids following the Arndt–Eistert methodology,[2] the hydrolysis of diyhdrouracils in alkaline solution,[3] the reaction of *N*-(1-alkoxyalkyl)carbamates with ester enolates,[4] and the condensation of imines with organomagnesium carboxylates.[5,6] The synthesis of β-amino ester derivatives has been also performed from 1,3,5-trialkyl-1,3,5-triazinanes[7–9] and *N,N*-bis-(trimethylsilyl)methoxymethylamine[10] by a titanium tetrachloride or a trifluoromethanesulfonate catalyzed amino-alkylation.

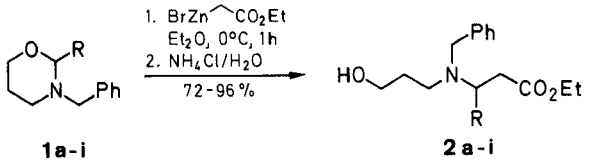
Although the Reformatsky reaction was intitially restricted to aldehydes or ketones,[11,12] it has been now extended to a great number of substrates.[13] In this way, β-amino acids or their derivatives can be prepared by reaction of zinc enolates[14,15] or organozinc carboxylates[16] with imines; the Reformatsky reaction applied to azomethines leads to β-lactams,[17,18] and recently, Katritzky has published a general preparation of β-amino esters by reaction of 1-alkyloxycarbonylamino-1-(1-benzotriazolyl)alkanes with ethyl 2-bromoalkanoates under Reformatsky-type conditions.[19] furthermore, β-amino esters have been obtained by reaction of α-amino ethers with α-bromo esters in the presence of magnesium or zinc,[20] and 7-hydroxy-3-aminoheptanenitriles from α-amino tetrahydropyrans and α-bromonitriles and zinc.[21]

Although nucleophilic ring opening of oxazolidines is a well-documented process,[22] homologous 1,3-oxazinanes have received less attention. Recently, we have shown that they are excellent starting materials in the synthesis of 3-dialkylaminopropanol derivatives and alkyl 3-dialkyl aminopropyl ethers by lithium aluminum hydride reduction.[22] We have now extended our studies to the regioselective ring opening of these substrates by Reformatsky reagents.

3-Benzyl-1,3-oxazinanes **1a–k**, obtained by condensation of 3-(benzylamino)propanol and the corresponding aldehyde, are reacted with the organozinc derivative, ethyl bromozincioacetate, previously prepared[23] from ethyl 2-bromoacetate and zinc dust, affording the β-amino ester derivatives **2a–k** in high yield.

As expected, the ring opening of the heterocyclic ring occurs by regioselective cleavage of the hemiacetal carbon–oxygen bond. We have also attempted to prepare the corresponding ethyl alkoxyalkanoates, by reaction of 3-methyl-5,6-dihydro-4*H*-1,3-oxazinium iodides with ethyl bromozincioacetate, taking into account the previously described regioselective cleavage of the carbon–nitrogen bond by lithium aluminum hydride in these salts.[22] However 3-methyl-5,6-dihydro-4*H*-1,3-oxazinium iodides are unable to react with ethyl α-bromoacetate and zinc, in diethyl ether, anhydrous tetrahydrofuran or dioxan; the starting materials are recovered unchanged after 24 hours at reflux in these solvents.

This new general approach is suitable for the preparation of both aliphatic and aromatic β-amino ester derivatives in high yield, from easily accessible starting materials, and using very mild conditions.



1a-i **2a-i**

1, 2	R	1, 2	R
a	Me	**f**	$PhCH_2CH_2$
b	Et	**g**	Ph
c	*i*-Pr	**h**	$4\text{-}ClC_6H_4$
d	Bu	**i**	$4\text{-}MeOC_6H_4$
e	*i*-Bu		

Table 1. β-Amino Esters **2** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula of 3,5-DNB[c]
2a	72	oil (69–70)[d]	$C_{23}H_{27}N_3O_8$ (473.4)
2b	77	oil (67–68)[d]	$C_{24}H_{29}N_3O_8$ (487.5)
2c	78	oil (91–92)[e]	$C_{25}H_{31}N_3O_8$ (501.5)
2d	95	oil (81–82)[e]	$C_{26}H_{33}N_3O_8$ (515.5)
2e	87	oil (98–99)[e]	$C_{26}H_{33}N_3O_8$ (515.5)
2f	96	oil (74–75)[e]	$C_{30}H_{33}N_3O_8$ (563.6)
2g	83	oil (93–94)[d]	$C_{28}H_{29}N_3O_3$ (535.5)
2h	87	oil (98–99)[e]	$C_{28}H_{28}ClN_3O_8$ (569.9)
2i	87	oil (74–75)[d]	$C_{29}H_{31}N_3O_9$ (565.5)

[a] Yields of isolated pure products.
[b] Numbers in parenthesis refer to melting point of the 3,5-dinitrobenzoates (3,5-DNB).
[c] Satisfactory microanalyses for 3,5-DNB: C ±0.13, H ±0.16, N ±0.14.
[d] From hexane.
[e] From hexane/toluene.

3-Benzyl-1,3-oxazinanes were synthesized from 3-(benzylamino) propanol as previously described.[22] The Reformatsky reagent was prepared as a ca. 0.6 M solution in anhydrous Et_2O from ethyl α-bromoacetate and zinc dust by a literature method.[23,24] IR were recorded on a Pye-Unicam SP-1000 spectrophotometer as neat film;

Table 2. Spectral Data for β-Amino Esters **2** Prepared

Product	IR (neat) ν_{OH}, ν_{CO} (cm^{-1})	^1H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
2a	3400, 1710	1.05 (d, 3H, $J = 6$, 4-CH_3), 1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.65 (m, 2H, NCH_2CH_2), 2.40 (m, 4H, 2-CH_2, NCH_2), 3.10 (m, 1H, 3-CH), 3.20 (br s, 1H, OH), 3.40 (m, 2H, $HOCH_2$), 3.50 (s, 2H, CH_2Ph), 4.05 (q, 2H, $J = 7$, OCH_2CH_3), 7.20 (m, 5H_{arom})	279 (M^+, < 1), 91 (100)
2b	3400, 1715	0.95 (t, 3H, $J = 6$, 5-CH_3), 1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 4H, 4-CH_2, NCH_2CH_2), 2.45 (m, 4H, 2-CH_2, NCH_2), 3.00 (m, 1H, 3-CH), 3.30 (br s, 1H, OH), 3.45 (m, 2H, $HOCH_2$), 3.55 (s, 2H, CH_2Ph), 4.00 (q, 2H, $J = 7$, OCH_2CH_3), 7.15 (m, 5H_{arom})	264 ($M^+ - 29$, 1) 91 (100)
2c	3400, 1715	0.95 (d, 6H, $J = 6$, $(CH_3)_2CH$), 1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 3H, 4-CH, NCH_2CH_2), 2.40 (m, 4H, 2-CH_2, NCH_2), 2.90 (m, 1H, 3-CH), 3.20 (br s, 1H, OH), 3.45 (s, 2H, CH_2Ph), 3.60 (m, 2H, $HOCH_2$), 4.05 (q, 2H, $J = 7$, OCH_2CH_3), 7.20 (m, 5H_{arom})	264 ($M^+ - 43$, 1) 91 (100)
2d	3360, 1715	0.95 (t, 3H, $J = 6$, 6-CH_3), 1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 8H, $(CH_2)_3$, NCH_2CH_2), 2.40 (m, 4H, 2-CH_2, NCH_2), 2.45 (m, 1H, 3-CH), 3.20 (br s, 1H, OH), 3.45 (s, 2H, CH_2Ph), 3.55 (m, 2H, $HOCH_2$), 4.05 (q, 2H, OCH_2CH_3), 7.20 (m, 5H_{arom})	321 (M^+, 2), 91 (100)
2e	3400, 1715	0.85 (d, 3H, $J = 6$, CH_3CH), 0.95 (d, 3H, $J = 6$, CH_3CH), 1.10 (t, 3H, $J = 7$, CH_3CH_2O), 1.40–1.80 (m, 5H, NCH_2CH_2, 4-CH_2, 5-CH), 2.40 (m, 4H, 2-CH_2, NCH_2), 3.05 (m, 1H, 3-CH), 3.15 (br s, 1H, OH), 3.35 (m, 2H, $HOCH_2$), 3.40 (s, 2H, CH_2Ph), 4.00 (q, 2H, $J = 7$, OCH_2CH_3), 7.20 (m, 5H_{arom})	321 (M^+, 1), 91 (100)
2f	3400, 1715	1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 4H, 4-CH_2, NCH_2CH_2), 2.50 (m, 6H, 2-CH_2, 5-CH_2, NCH_2), 3.05 (m, 1H, 3-CH), 3.30 (d, 1H, $J = 14$, NCHPh), 3.50 (m, 2H, $HOCH_2$), 3.65 (d, 1H, $J = 14$, NCHPh), 3.95 (br s, 1H, OH), 4.05 (q, 2H, $J = 7$, OCH_2CH_3), 7.20 (m, 10H_{arom})	369 (M^+, < 1), 91 (100)
2g	3400, 1710	1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 2H, NCH_2CH_2), 2.55 (m, 4H, 2-CH_2, NCH_2), 3.05 (br s, 1H, OH), 3.20 (d, 1H, $J = 14$, NCHPh), 3.45 (m, 2H, CH_2OH), 3.60 (d, 1H, $J = 14$, NCHPh), 4.00 (q, 2H, $J = 7$, OCH_2CH_3), 4.30 (m, 1H, 3-CH), 7.20 (m, 10H_{arom})	341 (M^+, 3), 91 (100)
2h	3380, 1710	1.15 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 2H, NCH_2CH_2), 2.60 (m, 4H, 2-CH_2, NCH_2), 2.90 (br s, 1H, OH), 3.25 (d, 1H, $J = 14$, NCHPh), 3.45 (m, 2H, CH_2OH), 3.70 (d, 1H, $J = 14$, NCHPh), 4.00 (q, 2H, $J = 7$, OCH_2CH_3), 4.25 (m, 1H, 3-CH), 7.20 (m, 9H_{arom})	375 (M^+, 2), 91 (100)
2i	3320, 1710	1.10 (t, 3H, $J = 7$, CH_3CH_2O), 1.60 (m, 2H, NCH_2CH_2), 2.40 (br s, 1H, OH), 2.80 (m, 4H, 2-CH_2, NCH_2), 3.30 (d, 1H, $J = 15$, NCHPh), 3.60 (m, 2H, $HOCH_2$), 3.65 (d, 1H, $J = 15$, NCHPh), 3.70 (s, 3H, OCH_3), 4.00 (q, 2H, OCH_2CH_3), 4.35 (m, 1H, 3-CH), 6.80 (d, 2H, $J = 9$, m-H_{arom}), 7.10 (d, 2H, $J = 9$, o-H_{arom}), 7.20 (m, 5H_{arom})	367 (M^+, 3), 91 (100)

^1H-NMR were registered on a Bruker AC-80 at 80 MHz, and Mass spectra were measured on a Hewlett-Packard 5988-A mass spectrometer by electronic impact at 70 eV. Melting points (uncorrected) were taken using a Büchi apparatus, in a capillary open tube.

Reaction of 3-Benzyl-1,3-oxazinanes with Reformatsky Reagents; General Procedure:

To a solution of the corresponding 3-benzyl-1,3-oxazinane (5 mmol) in anhydrous Et_2O (10 mL), cooled to 0 °C, under N_2, is syringed a previously prepared 0.6 M solution (10 mL) of ethyl bromozincioacetate in the same solvent.[23,24] The mixture is stirred at 0 °C for 1 h and then hydrolyzed by addition of sat. aq NH_4Cl (10 mL). The aqueous layer is extracted with Et_2O (4 × 25 mL), the organic layers are washed with brine and dried ($MgSO_4$). After removal of the solvent, the oily residues are purified by filtration on a short column of silica gel (10 × 2 cm, 230–400 mesh), using EtOAc as solvent. Compounds **2a–i** are colorless oils, and are characterized by their spectral data, and mp and microanalyses of their 3,5-dinitrobenzoates (3,5-DNB).

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(1) Koster, W.H.; Cimarusti, C.M.; Sykes, R.B. in *Chemistry and Biology of β-Lactam Antibiotics*, Morin, R.B.; Gorman, M. (eds.), Academic Press, New York 1982, vol. 3.
(2) Jones, J.H. in *Comprehensive Organic Chemistry*, Sutherland, I.O. (ed.), Pergamon Press, Oxford, 1979, vol. 2, part 9, p. 834.
(3) Rachina, V.; Blagoeva, I. *Synthesis* **1982**, 967.
(4) Shono, T.; Kise, N.; Sanda, F; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231.
(5) Ivanov, D.; Vassiliev, G.; Ranayotov, I. *Synthesis* **1975**, 83.
(6) Blagoev, B.; Ivanov, D. *Synthesis* **1970**, 615.
(7) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1156.
(8) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1747.
(9) Ikeda, K.; Achiva, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 913.
(10) Okano, K.; Morimoto, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* **1984**, 883.
(11) Sriner, R.L. *Org. React.* **1942**, *1*, 1.
(12) Rathke, M.W. *Org. React.* **1975**, *22*, 423.
(13) For a recently review on Reformatsky reaction see: Fürstner, A. *Synthesis* **1989**, 571.
(14) Dardoize, F.; Moreau, J.L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1972**, 3841.
(15) Dardoize, F.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1974**, 939.
(16) Bellassoued, M.; Arous-Chtara, R.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *231*, 185.
(17) Odriozola, J.M.; Cossio, F.P.; Palomo, C. *J. Chem. Soc. Chem. Commun.* **1988**, 809.
(18) Cossio, F.P.; Odriozola, J.M.; Oiarbide, M.; Palomo, C. *J. Chem. Soc., Chem. Commun.* **1989**, 74.
(19) Katritzky, A.R.; Yannakopoulou, K. *Synthesis* **1989**, 747.
(20) Canceill, J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1965**, 903.
(21) Glacet, C.; Brocard, J.; Maciejewski, L. *Bull. Soc. Chim. Fr.* **1977**, 337.
(22) Alberola, A.; Alvarez, M.A.; Andrés, C.; González, A.; Pedrosa, R. *Synthesis* **1990**, 153, and references therein.
(23) Siegel, A.; Keckeis, H. *Monatsh. Chem.* **1953**, *84*, 910.
(24) Vaughan, W.R.; Bernstein, S.C.; Lorber, M.E. *J. Org. Chem.* **1965**, *30*, 1790.