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Synthesis of *N*-acyl-β-aminoalcohols from *N*-acyloxazolidinones mediated by sodium azide

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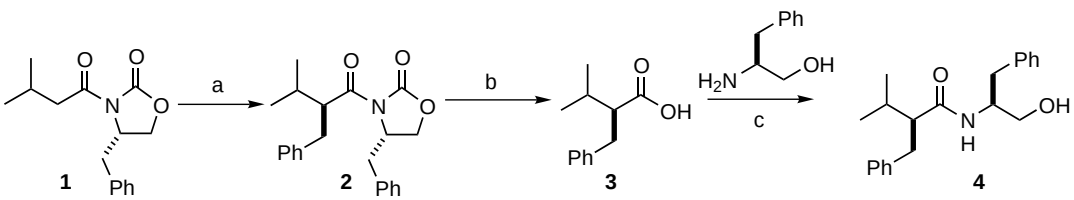
Abstract—*N*-Acyl-β-aminoalcohols were obtained efficiently via a highly endocyclic cleavage of *N*-acyloxazolidinones mediated by sodium azide in methanol at 40°C.

N-Acyloxazolidinones have found widespread application in the asymmetric syntheses.[1] In addition to their role as chiral auxiliaries, we studied *N*-acyloxazolidinones as potential protecting groups of *N*-acyl-β-aminoalcohols, which are found in several natural products[2] and in numerous drugs.[3] In this paper, we would like to report that the treatment of *N*-acyloxazolidinones with sodium azide in methanol afforded in high yields the corresponding *N*-acyl-β-aminoalcohols.

In connection with a program centered on HIV protease inhibitors, we needed a series of compounds containing *N*-acyl-β-aminoalcohol moiety as exemplified in **4** (Scheme 1). To prepare such a compound, we proceeded first by a two-step synthesis: hydrolysis of *N*-acyloxazolidinone **2** to the corresponding carboxylic acid **3** followed by standard EDC coupling of **3** with L-phenylalaninol to obtain the desired product **4**. Although this two-step synthesis provided good yields, we preferred a direct conversion of **2** to **4**. First attempts to hydrolyze **2** in an endocyclic manner with LiOH in THF/H_2O were unsuccessful and **4** was obtained in only 33% yield while the carboxylic acid **3** resulting from an exocyclic cleavage[4] was isolated as the major product in 55% yield. Other bases such as NaOH and KOH were attempted and gave identical results.

We found that the treatment of **2** with sodium azide in methanol at 40°C yielded within 6 h the alcohol **4** as the only reaction product in 95% yield (Scheme 2). Recently, Silverman and co-workers reported the hydrolysis of *p*-nitrobenzoic esters under the same conditions.[5] The intermediate carbonate **5** was isolated in 51% yield along with 22% of **4** when the reaction was conducted at room temperature for 24 h. Replacement of methanol with ethanol gave the carbonate **6** in 55% yield accompanied with 17% of **4**, whereas no reaction took place when isopropanol was employed as the solvent. The conversion of the carbonates **5** and **6** to **4** took place readily in the presence of water. The use of sodium azide is essential for the accomplishment of the oxazolidinone endocyclic cleavage and its replacement with diphenylphosphoryl azide or trimethylsilyl azide did not afford any trace of the desired β-hydroxyamide.



Scheme 1. *Reagents and conditions*: (a) NaHMDS, THF, BnBr, −40°C, 4 h, 91%, (b) LiOH, H_2O_2, H_2O/THF, 5 h, 75%, (c) EDC, $^iPr_2NEt$, CH_2Cl_2, 5 h, 72%.

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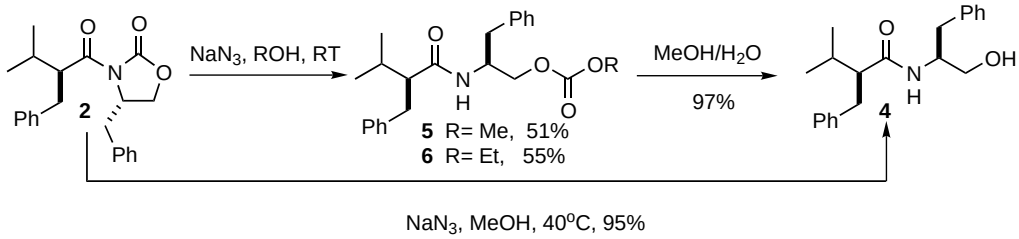


Scheme 2.

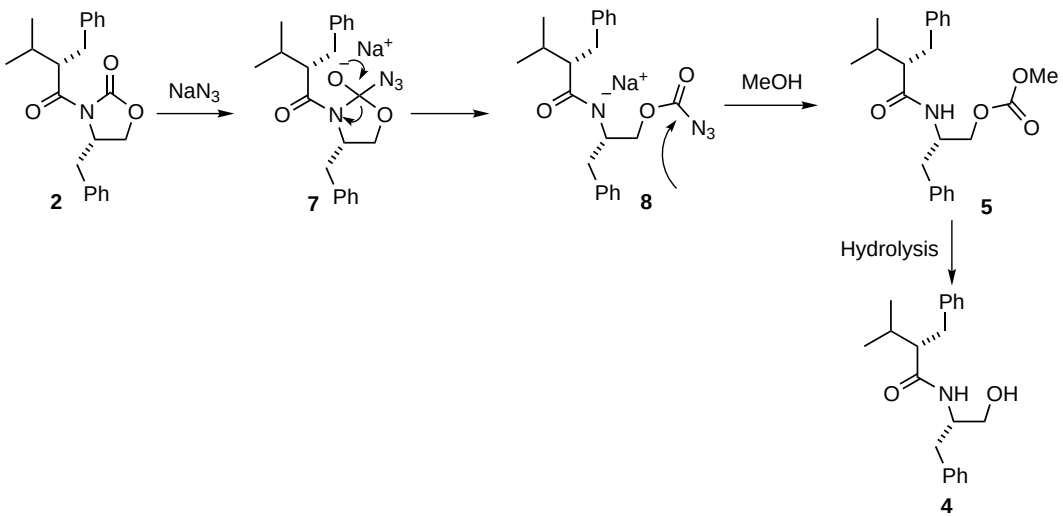
These results allowed us to gain insight into the reaction mechanism. As proposed in Scheme 3, a nucleophilic attack of sodium azide on the oxazolidinone carbonyl occurs to produce the tetrahedral intermediate **7**, which is followed by a ring opening to give **8**. Displacement of the azide group with methanol affords the carbonate **5**, which in the presence of water underwent hydrolysis to give **4**.

As depicted in Table 1, other oxazolidinone derivatives containing different auxiliary chirals and acyl groups were subjected to the action of NaN_3 in MeOH or in EtOH. High to excellent yields of *N*-acyl-β-aminoalcohols were isolated when the *N*-acyloxazolidinones are α-branched as in **9**–**12**. Moderate yields, however, were obtained in the case of unbranched *N*-acyloxazolidinones **13** and **1**. It is worth noting that the reaction is catalytic, as shown when it was carried out with only 0.1 equiv. of sodium azide (Table 1). The use of an excess of NaN_3 to reduce the reaction time was not inconvenient because it was easily separated from the reaction by aqueous workup.

Typical procedure for the preparation of *N*-acyl-β-aminoalcohols 4 from *N*-acyloxazolidinone 2: To a stirred solution of **2** (351 mg, 1 mmol) in methanol (15 mL) was added sodium azide (195 mg, 3 mmol). The reaction was stirred at 40°C until complete consumption of the starting material. To the suspension was added water (1 mL) and the resulting limpid solution was stirred for an additional 2 h. After cooling, the reaction was diluted with water and EtOAc. The aqueous layer was washed twice with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (EtOAc/hexanes = 1:1) to afford 380 mg of the β-hydroxyamide **4**.[6]

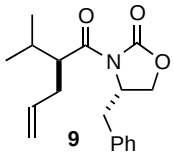
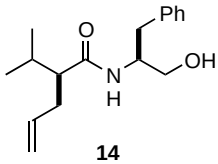
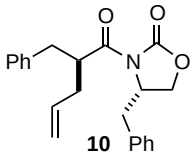
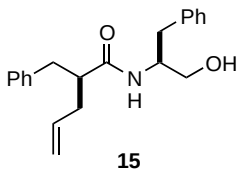
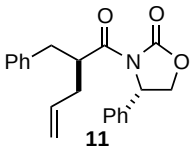
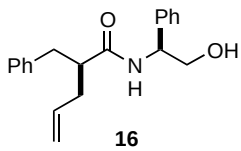
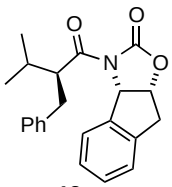
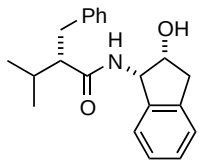
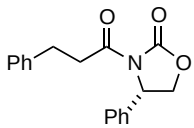
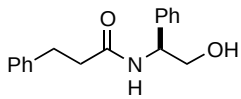
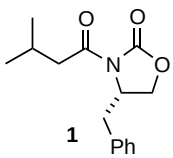
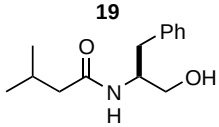
Typical procedure for the preparation of carbonate 5 from *N*-acyloxazolidinone 2: To a stirred solution of **2** (351 mg, 1 mmol) in methanol (15 mL) was added sodium azide (195 mg, 3 mmol). The reaction was stirred at room temperature for 24 h, then concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexanes = 1:4) to afford 195 mg of the carbonate **5**.[6]

In summary, *N*-acyl-β-aminoalcohols were obtained efficiently and under almost neutral conditions by endocyclic cleavage of *N*-acyloxazolidinone mediated by sodium azide in methanol or in ethanol at 40°C.[7]



Scheme 3.

Table 1. NaN_3-mediated endocyclic cleavage of *N*-acyloxazolidinone

N-Acyloxazolidinone	Conditions	N-Acyl-β-aminoalcohol	Yield[a]
 **9**	NaN_3 (3 eq), MeOH 40°C, 15 h	 **14**	91%
	NaN_3 (0.1 eq), MeOH 40°C, 4 days		66%
 **10**	NaN_3 (3 eq), MeOH 40°C, 8 h	 **15**	88%
 **11**	NaN_3 (3 eq), MeOH 40°C, 15 h	 **16**	92%
 **12**	NaN_3 (3 eq), MeOH 40°C, 20 h	 **17**	83%
 **13**	NaN_3 (3 eq), EtOH 40°C, 4h	 **19**	61%[b]
 **1**	NaN_3 (3 eq), EtOH 40°C, 8h	 **18**	75%

[a] Isolated yield after purification.
[b] *trans*-Esterification byproduct, $PhCH_2CH_2CO_2Et$, was isolated in 32% yield.

References

1. (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23; (b) Ager, D. J.; Prakash, I.; Shaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875; (c) Ager, D. J.; Prakash, I.; Shaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3–12.
2. See for example: (a) Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23–27; (b) Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L. Pena, M. *J. Org. Chem*, **1997**, *62*, 6420–6423; (c) Sarubbi, E.; Seneci, P. F.; Angelastro, M. R.; Peet, N. P.; Denaro, M.; Islam, K. *FEBS Lett*, **1993**, *319*, 253–256; (d) Stefanelli, S.; Cavaletti, L.; Sarubbi, E.; Colombo, L.; Selva, E. *J. Antibiot.* **1995**, *48*, 332–334.
3. See for example, HIV-protease inhibitor, Indinavir: (a) Dorsey, B. D.; McDonough, C.; McDaniel, S. L.; Levin, R.; Newton, C. L.; Hoffman, J. M.; Dark, P. L.; Zugay-Murphy, J. A.; Emini, E. A.; Schleif, W. A.; Olsen, D. B.; Stahlhut, M. W.; Rutkowsky, C. A.; Kuo, L. C.; Lin, J. H.; Chen, I.-W.; Michelson, S. R.; Holloway, M. K.; Huff, J. R.; Vacca, J. P. *J. Med. Chem.* **2000**, *43*, 3386–3399; (b) Perez, C.; Pastor, M.; Ortiz, A. R.; Gaco, F. *J. Med. Chem.* **1998**, *41*, 836–852.
4. (a) Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, 2369–2372; (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
5. Gomez-Vidal, J. A.; Forester, M. T.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2477–2479; Gomez-Vidal, J. A.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2480–2484. These two papers appeared while the present manuscript was in preparation.
6. Selected spectral data for compounds **4**, **5**, **14**, **15** and **18**. Compound **4**: White solid, ^1H NMR (500 MHz, $CDCl_3$) δ

0.96 (d, $J=6.4$ Hz, 3H), 1.05 (d, $J=5.5$ Hz, 3H), 1.96 (m, 2H), 2.40 (bs, 1H, OH), 2.50 and 2.58 (ABX, $J=13.5$ and 7.0 Hz, 2H), 2.82–2.93 (m, 2H), 3.42 and 3.50 (ABX, $J=11.2$ and 5.6 Hz, 2H), 3.99 (m, 1H), 5.38 (d, $J=6.3$ Hz, 1H, NH), 6.96 (d, $J=7.1$ Hz, 2H), 7.17–7.29 (m, 8H). MS (CI, NBA) m/z (%) 326 (MH^+, 100). Compound **5**: White solid, ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, $J=7.1$ Hz, 3H), 1.05 (d, $J=6.6$ Hz, 3H), 1.93 (m, 2H), 2.35 and 2.55 (ABX, $J=13.8$ and 7.5 Hz, 2H), 2.88 (m, 2H), 3.77 (s, 3H, Me), 3.90 and 3.96 (ABX, $J=11.2$ and 5.6 Hz, 2H), 4.37 (m, 1H), 5.26 (d, $J=8.6$ Hz, 1H, NH), 6.90 (d, $J=7.0$ Hz, 2H), 7.18–7.29 (m, 8H). MS (CI, NBA) m/z (%) 384 (MH^+, 84), 308 (100). Compound **14**: White solid, ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, $J=6.4$ Hz, 3H), 0.92 (d, $J=6.5$ Hz, 3H), 1.73 (m, 2H), 2.20 (m, 2H), 2.80 and 2.90 (ABX, $J=13.5$ and 7.5 Hz, 2H), 3.40 (bs, 1H, OH), 3.62 (ABX, $J=13.4$ and 7.3 Hz, 2H), 4.20 (m, 1H), 4.83–5.00 (m, 2H), 5.50 (m, 1H), 6.00 (d, $J=6.4$ Hz, 1H, NH), 7.15–7.35 (m, 5H). MS (CI, NBA) m/z (%) 276 (MH^+, 100), 258 (11), 154 (42). HRMS calcd for $C_{17}H_{26}NO_2$ 276.196335, found 276.19680. Compound **15**: White solid, ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (bs, 1H, OH), 2.20 (m, 1H), 2.30 (m, 1H), 2.41 (m, 1H), 2.65 and 2.85 (ABX, $J=13.2$ and 7.2 Hz, 2H), 2.78 (dd, $J=13.2$ and 6.1 Hz, 2H), 3.35 (ABX, $J=13.0$ and 7.1 Hz, 2H), 4.08 (m, 1H), 4.94 (d, $J=10.0$ Hz, 1H), 5.01 (d, $J=15.0$ Hz, 1H), 5.38 (d, $J=6.3$ Hz, 1H, NH), 5.50–5.62 (m, 1H), 7.10–7.32 (m, 10H). MS (CI, NBA) m/z (%) 324 (MH^+, 100), 306 (42). Compound **18**: White solid, ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, $J=6.3$ Hz, 3H), 0.90 (d, $J=6.5$ Hz, 3H), 1.95–2.07 (m, 2H), 2.82 and 2.90 (ABX, $J=13.5$ and 7.5 Hz, 2H), 3.00 (bs, 1H, OH), 3.60 (dd, $J=13.0$ and 7.0 Hz, 1H), 3.70 (d, $J=11.2$ Hz, 1H), 4.20 (m, 1H), 5.83 (d, $J=1$H, NH), 7.20–7.32 (m, 5H), MS (CI, NBA) m/z (%) 236 (MH^+, 100), 218 (33).

7. All compounds were characterized by ^1H NMR and MS and are consistent with the assigned structures.