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# Decarboxylative Isomerization of *N*-Acyl-2-oxazolidinones to 2-Oxazolines

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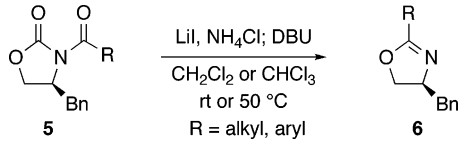
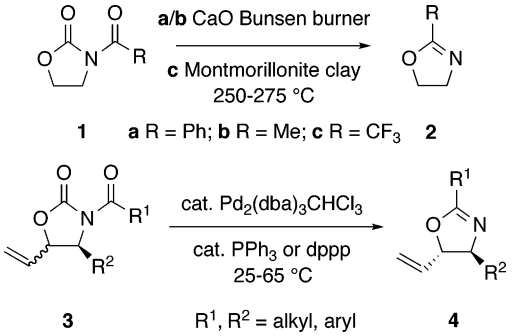



*N*-Acyl-2-oxazolidinones are ring-opened by lithium iodide and decarboxylated in the presence of a mild proton source. Further reaction with an amine base provides 2-oxazolines. The transformation is general for oxazolidinones unsubstituted in the 5 position and occurs under mild conditions (25−50 °C). These results complement the existing methods for this transformation by allowing lower temperatures and/or avoiding metal catalysts.

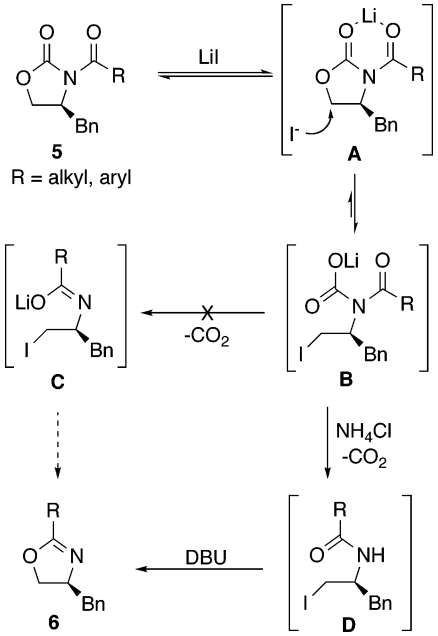
Oxazolines comprise a number of biologically active natural products and medicinal compounds.[1,2] Their well-documented use as ligands in asymmetric catalysis, as well as their wide use as monomers in living cationic polymerization, makes multiple methods for their synthesis attractive.[3,4] We describe here a one-pot procedure for the conversion of *N*-acyl-2-oxazolidinones to 2-substituted oxazolines by a lithium iodide/ammonium chloride/DBU-mediated decarboxylative cyclization.

Previous one-pot transformations of this type are outlined in Scheme 1. In the presence of an equal weight of CaO, *N*-benzoyloxazolidinone **1a** was converted to **2a** in 65% yield by heating with a Bunsen burner in the absence of solvent.[5a] This method appears to have a limited substrate scope; for example, *N*-acetyloxazolidinone **1b** under these conditions gave product **2b** having purity of only 25%. Another high-temperature method, applied only to the trifluoroacetyl derivative **1c**, gave **2c** in 76% yield.[5b] A palladium-catalyzed transformation of 5-vinyl-substituted oxazolidinones **3** to oxazolines **4** has been reported.[6] Yields and diastereoselectivities are high for this process, but the requirement of a 5-alkenyl substituent is a limitation of this chemistry. The drawbacks of the previous methods caused us to search for an alternative that did not require high temperatures or expensive catalysts while still allowing a variety of *N*-acyl substituents.

**SCHEME 1. Decarboxylative Cyclizations of *N*-Acyloxazolidinones**




**SCHEME 2. Lithium Iodide Initiated Decarboxylative Cyclization**




The initial notion was that a decarboxylative cyclization requiring only catalytic amounts of lithium iodide might be achieved as outlined in Scheme 2. Attack at the 5 position of activated oxazolidinone **A** by iodide would give the lithium carboxylate **B**, which we hoped would decarboxylate to the lithium amide **C** and *O*-alkylate to give oxazoline **6**, thereby regenerating lithium iodide.[7] Indeed, 4-phenylmethyl-2-oxazolidinone **5d** (R = Ph) reacted with lithium iodide under mild

(1) Bertram, A.; Pattenden, G. *Nat. Prod. Rep.* **2007**, *24*, 18−30.
(2) Pirrung, M. C.; Tumey, L. N.; McClerran, A. L.; Raetz, C. R. H. *J. Am. Chem. Soc.* **2003**, *125*, 1575−1586.
(3) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561−3651.
(4) Kobayashi, S.; Uyama, H.; Narita, Y.; Ishiyama, J. *Macromolecules* **1992**, *25*, 3232−3236.
(5) (a) Mundy, B. P.; Kim, Y. *J. Heterocycl. Chem.* **1982**, *19*, 1221−1222. (b) Foris, A.; Neumer, J. F. *Magn. Reson. Chem.* **2005**, *43*, 867−868.
(6) (a) Cook, G. R.; Shanker, S. P. *J. Org. Chem.* **2001**, *66*, 6818−6822. (b) Cook, G. R.; Shanker, S. P. *Tetrahedron Lett.* **1998**, *39*, 3405. (c) Cook, G. R.; Manivannan, E.; Underdahl, T.; Lukacova, V.; Zhang, Y.; Balaz, S. *Bioorg. Med. Chem. Lett.* **2004**, *19*, 4935−4939.
(7) Intervention of *N*-alkylation to generate an *N*-acylaziridine cannot be excluded since, via the Heine rearrangement, these are known to ring open and isomerize to 2-oxazolines in the presence of iodide ion: (a) Heine, H. W.; Kenyon, W. G.; Johnson, E. M. *J. Am. Chem. Soc.* **1961**, *83*, 2570−2574. (b) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: London, 2005; pp 198−199.

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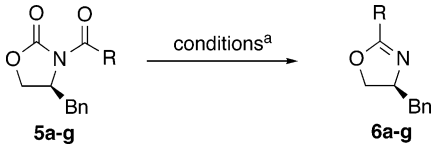
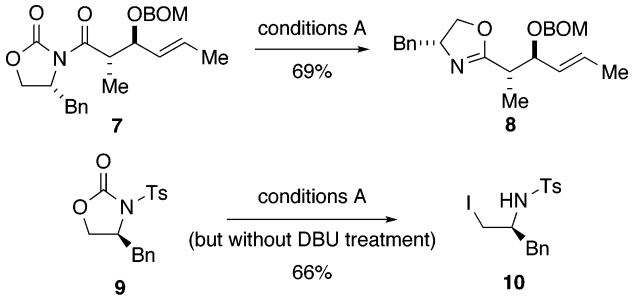
**TABLE 1. Decarboxylative Cyclizations of *N*-Acyloxazolidin-2-ones 5 to Oxazolines 6**




| entry | R | conditions[a] | yield (%)[b] |
|---|---|---|---|
| **a** | Me | A | 62[c] |
| **b** | Et | A | 71 |
| **c** | $^{i}$Pr | A | 82 |
| **d** | Ph | B | 76 |
| **e** | 4-MeOC$_6$H$_4$ | B | 73[d] |
| **f** | 4-NO$_2$C$_6$H$_4$ | B | 45 |
| **g** | 2-napthyl | B | 80 |

[a] A: LiI (4.0 equiv), $NH_4Cl$ (2.0 equiv), 0.2 M in $CHCl_3$, 50 °C, 16 h; DBU (3.0 equiv), rt, 6 h. B: LiI (2.0 equiv), $NH_4Cl$ (2.0 equiv), 0.2 M in $CH_2Cl_2$, rt, 12 h; DBU (3.0 equiv), rt, 6 h. [b] Isolated yield after chromatography. [c] With 10% recovered deacylated **5a**. [d] Yield of 81% based on recovered starting material.

**SCHEME 3. Additional Lithium Iodide Initiated Reactions**




BOM = benzyloxymethyl

conditions (ambient temperature, DCM), but the overall plan was thwarted when intermediate **B** failed to decarboxylate. That is, in the presence of substoichiometric amounts of LiI, the reaction never proceeded to completion, and (labile) intermediate **D** (R = Ph) could be observed (NMR spectroscopy) after protic workup. This crude iodoamide could be subsequently cyclized efficiently to oxazoline **6d** (R = Ph) by the action of DBU. We were pleased to see that incorporation of a weak proton source (e.g., $NH_4Cl$) in the reaction mixture from the outset caused in situ decarboxylation. We then found that, if DBU was added after full conversion of **5** to **D**, all three steps could be performed easily in one pot. If DBU was present from the outset, **5** was consumed much more slowly, presumably because of the reduced Lewis acidity resulting from competitive complexation of $Li^+$ by DBU. Finally, when pure **6d** was subjected to LiI (with and without added $NH_4Cl$) in DCM in the absence of DBU, it did not revert to **D**, demonstrating that the cyclization of **D** to **6** is not reversible.

After screening for the best choice of solvent, concentration, reaction time, proton source, metal additive, and follow-up base, we settled upon one-pot conditions in which the 2-oxazolidinone **5** was first treated with LiI and $NH_4Cl$ in a chlorocarbon solvent and, after complete consumption of **5** (TLC), DBU (3 equiv) was added. Results from the decarboxylation/cyclization of *N*-alkanoyloxazolidinones **5a**−**c** (conditions A) and *N*-aroyloxazolidinones **5d**−**g** (conditions B) are summarized in Table 1. For the latter set, less lithium iodide (2 vs 4 equiv) was used, and the reaction was typically carried out at room temperature rather than 50 °C.

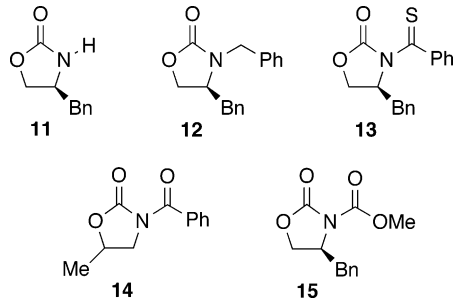



**FIGURE 1.** Unsuitable decarboxylative cyclization substrates.

Substrate scope was explored (Scheme 3 and Figure 1). The aldol adduct **7** was a suitable substrate for ring opening, giving the oxazoline **8** in 69% yield after chromatography.[8] It is noteworthy that no epimerization of the α stereocenter was observed during the decarboxylation or cyclization steps,[9] making this the method of choice for producing 2-oxazolines with a stereocenter at the α position of the C2 substituent.[10] Sulfonimide **9** gave rise to the iodoalkylsulfonamide **10** in 66% yield following ring opening and decarboxylation.[11,12]

Shown in Figure 1 are substrates that did not cleanly (if at all) ring open with the iodide ion. In the case of attempted aziridine formation with unactivated substrates **11** and **12**, little to no conversion of the starting material was observed, even under forcing conditions.[13] The lack of reactivity speaks to both the chelating and electron-withdrawing property of the *N*-acyl substituent in the successful cyclizations. In the case of *N*-thiocarbonyl compound **13**, poor conversion to product is observed, presumably owing to the lower Lewis basicity of sulfur.[14] Substitution on the 5 position of the oxazolidinone as in substrate **14** was found to effectively shut down the iodide-initiated decarboxylation, a result that was not unexpected considering the mechanism of the reaction. Interestingly, the *N*-methoxycarbonyl compound **15** was found to be unsuitable for the reaction; instead, it underwent demethylation by iodide and decarboxylation to give methyl iodide ($^1$H NMR) and **11**.

In conclusion, the transformation of *N*-acyl-2-oxazolidinones to 2-oxazolines is afforded by a one-pot reaction with lithium iodide/$NH_4Cl$ followed by DBU. The conditions are mild and general for oxazolidinones unsubstituted in the 5 position. These results expand the methodology of decarboxylative cyclization chemistry. This method is potentially valuable to those interested in making oxazoline ligands for asymmetric catalysis, monomers

(8) For the synthesis of *anti*-aldol adducts, see: Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393.

(9) As judged from the fact that the $^1$H NMR spectrum of the oxazoline product **8** indicated that it was essentially one diastereomer.

(10) For general reviews on oxazoline formation and usage, see: (a) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483−505. (b) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837−860. (c) Kronek, J.; Luston, J.; Boehme, F. *Chem. Listy* **1998**, *92*, 175−185.

(11) Hedayatullah, M.; Brault, J. F. *Phosporus Sulfur* **1981**, *11*, 303−310.

(12) Treatment of **10** with DBU led to consumption and generation of baseline TLC material. Although this was not further explored, the presumed intermediate tosylaziridine would be expected to undergo ring opening by the nucleophilic DBU to form an ammonium salt: Moon, B.; Han, S.; Kim, D. *Org. Lett.* **2005**, *7*, 3359−3361.

(13) We are aware of a single example of aziridine formation from an *N*-alkyloxazolidinone in which TMSI was used as the reagent. See: Lakanen, J. R.; Pegg, A. E.; Coward, J. K. *J. Med. Chem.* **1995**, *38*, 2714−2727.

(14) For the synthesis of thioacylated carbamates, see: Wagner, G.; Leistner, S. *Pharmazie* **1972**, *27*, 547−552.

for living cationic polymerization, or potential bioactive/medicinal compounds.[1−4]

## Experimental Section

**Conditions B: The Decarboxylative Cyclization of 5d to give 6d.** To a 6 mL screw cap vial equipped with a stirbar were added 0.0596 g (0.212 mmol) of (*S*)-3-benzoyl-4-phenylmethyl-2-oxazolidinone (**5d**), 0.0590 g (0.440 mmol) of lithium iodide, 0.0233 g (0.440 mmol) of ammonium chloride, and 1.1 mL of methylene chloride. The vial was then capped, and the mixture was stirred at room temperature for 12 h. DBU (0.095 mL, 0.637 mmol) was added. After 6 h, the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (40% EtOAc in hexanes) to afford 0.0381 g (76%) of the desired product as a clear oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.59−7.94 (m, 2H), 7.50−7.47 (m, 1H), 7.43−7.40 (m, 2H), 7.33−7.29 (m, 2H), 7.26−7.23 (m, 3H), 4.58 (dddd, $J$ = 9.0, 9.0, 7.5, 5.0 Hz, 1H), 4.35 (dd, $J$ = 9.0, 9.0 Hz, 1H), 4.15 (dd, $J$ = 8.0, 8.0 Hz, 1H), 3.25 (dd, $J$ = 14.0, 5.5 Hz, 1H), and 2.73 (dd, $J$ = 14.0, 9.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 164.0, 137.9, 131.3, 129.6, 128.5, 128.3, 128.2, 126.5, 71.8, 67.9, and 41.8; HRMS (ESI) calcd for ($C_{16}H_{15}NO + Na^+$) 260.1046, found 260.1066; GC−MS $t_r$ = 12.0 min; *m*/*z* 237, 218, 206, 146, 118, 105, 91, 77, 65, and 51; IR (neat) 3061, 3027, 2960, 2929, 2899, 1651, 1603, 1579, 1495, 1455, 1450, 1358, 1085, 1060, 1025, 967, 780, and 695 cm$^{-1}$; TLC $R_f$ = 0.50 in 30% EtOAc in hexanes; $[\alpha]^{rt}$ = +8.0 ($c$ = 0.670, $CHCl_3$).

**Conditions A: The Decarboxylative Cyclization of 7 to give 8.** To a 6 mL screw cap vial equipped with a stirbar were added 0.0374 g (0.0884 mmol) of (4*R*)-3-[(2*S*,3*S*,4*E*)-2-methyl-1-oxo-3-phenylmethoxymethoxy-4-hexenyl]-4-phenylmethyl-2-oxazolidinone (**7**), 0.0575 g (0.429 mmol) of lithium iodide, 0.0105 g (0.198 mmol) of ammonium chloride, and 0.33 mL of chloroform. The vial was then capped, and the mixture was stirred at 50 °C in an oil bath for 12 h. After allowing the reaction mixture to cool to room temperature, 0.049 mL (0.329 mmol) of DBU was added. After 6 h at room temperature, the mixture was filtered through a plug of silica gel (EtOAc eluent) before being purified by medium pressure liquid chromatography (30% EtOAc in hexanes) to afford 0.0231 g (69%) of the desired product as a clear oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.25 (m, 7H), 7.22−7.17 (m, 3H), 5.75 (dq, $J$ = 15.0, 6.5 Hz, 1H), 5.26 (ddq, $J$ = 15.5, 9.0, 2.0, 2.0, 2.0 Hz, 1H), 4.81 (d, $J$ = 7.0 Hz, 1H), 4.675 (d, $J$ = 7.5 Hz, 1H), 4.674 (d, $J$ = 11.5 Hz, 1H), 4.45 (d, $J$ = 11.5 Hz, 1H), 4.38 (dddd, $J$ = 9.5, 9.5, 7.5, 5.0 Hz, 1H), 4.22 (dd, $J$ = 9.0, 8.5 Hz, 1H), 4.09 (dd, $J$ = 9.5, 8.5 Hz, 1H), 3.94 (dd, $J$ = 8.5, 7.5 Hz, 1H), 3.14 (dd, $J$ = 13.5, 4.5 Hz, 1H), 2.72 (dq, $J$ = 7.0, 7.5 Hz, 1H), 1.73 (dd, $J$ = 6.5, 2.0 Hz, 3H), and 1.11 (d, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 169.5, 138.2, 132.3, 129.4, 128.7, 128.6, 128.5, 128.1, 127.8, 126.6, 115.1, 91.4, 78.7, 71.7, 69.3, 67.3, 42.0, 39.1, 18.0, and 14.3; HRMS (ESI) calcd for ($C_{24}H_{30}NO_3^+$) 380.2220, found 380.2289; GC−MS $t_r$ = 14.7 min; *m*/*z* 379, 355, 341, 327, 288, 258, 243, 242, 228, 218, 207, 188, 161, 150, 117, 91, and 65; IR (neat) 3030, 2939, 2885, 1667, 1654, 1505, 1455, 1383, 1174, 1100, 1036, 1027, 971, 924, 733, and 698 cm$^{-1}$; TLC $R_f$ = 0.50 in 40% EtOAc in hexanes; $[\alpha]^{rt}$ = +70.5 ($c$ = 0.210, $CHCl_3$).

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**Supporting Information Available:** Experimental procedures and full characterization data and copies of the $^1$H and $^{13}$C NMR spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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