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A facile synthesis of 2-oxazolidinones via Hofmann rearrangement mediated by bis(trifluoroacetoxy)iodobenzene

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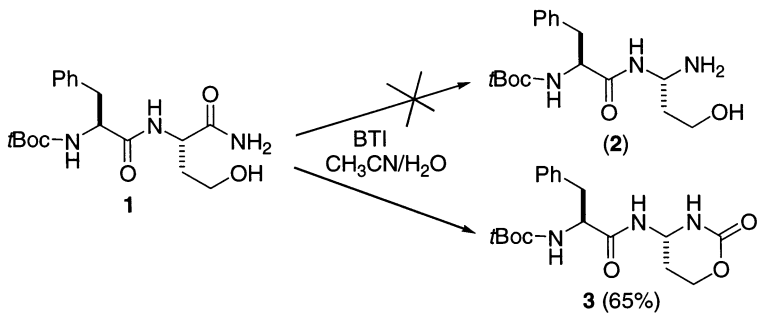
Abstract—A mild and efficient synthesis of 2-oxazolidinones from β-hydroxypropionamides via Hofmann rearrangement was achieved in 96% to quantitative yield using bis(trifluoroacetoxy)iodobenzene (BTI) in acetonitrile. The method should be useful in both solution- and solid-phase construction of 2-oxazolidinone libraries. © 2001 Published by Elsevier Science Ltd.

Chiral 2-oxazolidinones (Evans' chiral auxiliaries) are widely used as auxiliaries for asymmetric transformations in organic synthesis.[1] Methodologies using chiral 2-oxazolidinones have been highly successful in the stereoselective construction of a number of natural products, antibiotics, and other medicinally important compounds with antidepressant, antihistaminic, antifungal, antihypertensive, or antibacterial activity.[2–5] However, current methods for the preparation of 2-oxazolidinones require the use of a strong base (e.g. *n*-BuLi, NaH) and an aqueous work-up.[6] The processes often involve the use of very low and very high temperatures[7] and the use of toxic reagents such as phosgene, diphosgene, triphosgene, and isocyanates.[2] These limitations make it difficult to adapt these conditions for the construction of combinatorial libraries of 2-oxazolidinones which have become important in drug discovery research.[8] Here, we wish to describe a mild condition for the facile synthesis of 2-oxazolidinones that can be easily adapted for the construction of 2-oxazolidinone libraries.

In our research, we needed to convert γ-hydroxybutyramide **1** to γ-aminoalcohol (**2**) via a Hofmann rearrangement (Scheme 1). After surveying the literature, we decided to use the mild bis(trifluoroacetoxy)iodobenzene (BTI) reagent to effect the Hofmann rearrangement in a mixed solvent of acetonitrile and water.[7] To our surprise, γ-hydroxybutyramide **1** under this condition failed to give the desired product **2** but rearranged and cyclized to form 1,3-oxazinan-2-one **3**[9] as the major product in 65% yield. Apparently, the predominant reaction under this condition was an intramolecular nucleophilic attack by the neighboring hydroxyl group rather than the expected nucleophilic attack by a solvent water molecule.



Scheme 1.

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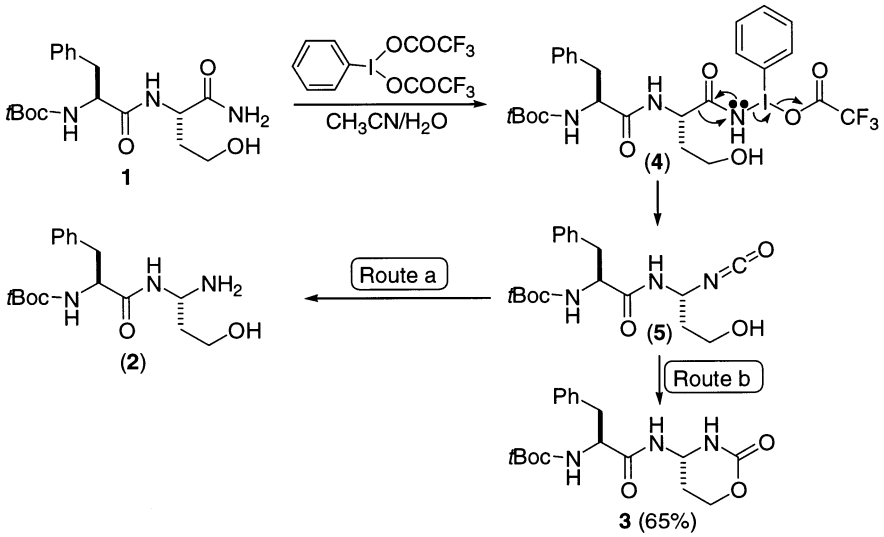
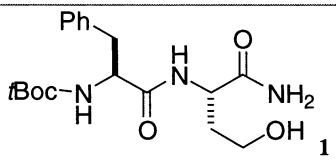
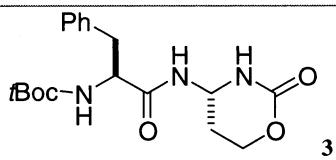
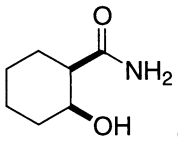
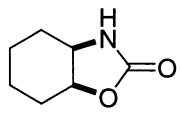
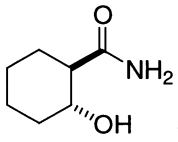
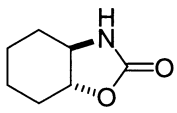
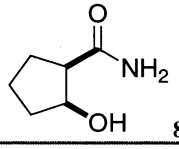
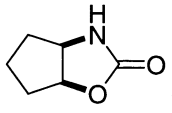


Scheme 2.

Scheme 2 shows the reaction pathways that could lead to the formation of the two potential products. The isocyanate intermediate **(5)**, the common intermediate after rearrangement of the BTI adduct **(4)**, could be hydrolyzed in the presence of water to produce the amine product **2** (route a) or undergo an intramolecular nucleophilic-addition reaction to give the cyclized product **3** (route b). In our case, the isocyanate **(5)** was found to produce preferentially the cyclized 1,3-oxazinan-2-one **3**, suggesting that the entropically favored intramolecular cyclization to form a 6-membered ring system is much faster than the intermolecular hydrolysis by the solvent water molecule.[10]

This simple Hofmann rearrangement reaction of γ-hydroxybutyramide **1** to 1,3-oxazinan-2-one **3** was very clean in acetonitrile/water, but the yield of isolated product was only 65%. We found that excess water could lead to decomposition of the reagent BTI. Indeed, by replacing the mixed solvent of acetonitrile and water with neat acetonitrile, we were able to increase the yield of the cyclized product from 65% to quantitative yield (Table 1). Later, we found that reagent grade acetonitrile was sufficient for this process in terms of both the yield and the reproducibility. Thus, no stringent anhydrous conditions or techniques were necessary for the success of this reaction. Because

Table 1. Hofmann rearrangement of amides by treatment with BTI[a]

Substrate[b]	Conc. (M)	Time (h)	Product	Yield %[c]
 **1**	0.1	2	 **3**	100
 **6**	0.2	1.5	 **9**	96
 **7**	0.2	4.5	 **10**	100
 **8**	0.1	4	 **11**	98

[a] All reactions were carried out in reagent grade acetonitrile at room temperature.
[b] Substrates 6-8 used were racemic; [c] Isolated yields.

Table 2. Effect of solvent on the Hofmann rearrangement of **6**[a]

Entry	Solvent	Yield (%)[b]
1	CH_3CN	96
2	CH_2Cl_2	41
3	DMF	95
4	DMSO	5
5	Toluene	45
6	THF	80
7	Et_2O	27
8	Dioxane	35

[a] General condition: **6** (1 mmol, 0.2 M), TIB (1 mmol), rt, 1.5 h.
[b] Isolated yields.

iodobenzene derived from reagent BTI is significantly less polar than 1,3-oxazinan-2-one **3**, it can be washed off readily using hexanes, or removed easily by Kugelrohr distillation if the reaction is run on a large scale. We reasoned that this condition could be developed into a mild practical method for the construction of 2-oxazolidinone libraries starting from β-hydroxypropionamides.

As shown in Table 1, we ran the same reaction starting from several commercially available β-hydroxypropionamides and demonstrated the general synthetic usefulness of this process. The typical procedure we developed is as follows: To a solution of β-hydroxypropionamide (1 mmol) in reagent grade acetonitrile (5 mL) was added stoichiometric amount of BTI (1 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After the disappearance of starting material, the solvent was removed under reduced pressure and the residue purified to give the desired product by flash column chromatography using an initial wash with hexanes to remove iodobenzene followed by elution of the desired product.[11]

Table 3. Effect of substrate concentration and temperature on the Hofmann rearrangement[a]

Reaction condition		Product yield (%)[b]		
		6→9	**7→10**	**8→11**
Concentration[c]	0.05 M	72	78	74
	0.10 M	85	83	94
	0.20 M	97	91	80
	0.30 M	64	74	66
Temperature[d]	0°C	57	49	51
	25°C	97	91	94
	50°C	90	81	83

[a] General condition: substrate (1 mmol), TIB (1 mmol), CH_3CN.
[b] Isolated yields were based on the reaction outcome within 2 h.
[c] The effect of substrate concentration was studied at 25°C.
[d] The effect of temperature was studied for substrates **6**, **7**, and **8** at concentrations of 0.2, 0.2, and 0.1 M, respectively.

All products listed in Table 1 were identified by ^1H NMR, ^{13}C NMR, and LC-MS.[12] Under the treatment of BTI, *cis*-2-aminocyclohexanecarboxylic acid amide **6** and its *trans* isomer **7** were converted to their corresponding *cis*-hexahydrobenzoxazol-2-one **9**[13] and *trans*-isomer **10**[13] in 96% and 100% yields, respectively. Similarly, treatment of *cis*-2-aminocyclopentanecarboxylic acid amide **8** with 1 equivalent of BTI afforded *cis*-hexahydrocyclopentaoxazol-2-one **11**[14] in 98% yield.

We also explored the effect of solvent on the reaction yield. As shown in Table 2, acetonitrile was found to be the solvent of choice. It has several advantages over other solvents. It effectively dissolves a broad range of organic compounds. It is less toxic than most of the other solvents such as dichloromethane and ethyl ether. It is more easily removed by evaporation than other commonly used solvents of high boiling points such as DMF, toluene, and dioxane. Reactions using acetonitrile as the solvent are easily monitored using HPLC since acetonitrile is frequently used as an eluting solvent in HPLC. This makes it possible for the high-throughput HPLC analysis of reaction mixtures that might be needed in combinational synthesis.

Our study also indicated that optimal substrate concentration for this reaction is 0.1–0.2 M and that concentrations beyond this range would adversely affect the rate and yield of this reaction (Table 3). Room temperature was found to be sufficient for this reaction since elevated temperature did not significantly increase the rate of rearrangement and might induce other side reactions.

In comparison to previous methods for the synthesis of 2-oxazolidinones, our method using BTI in acetonitrile is milder and highly efficient. The only procedure in the literature for the conversion of β-hydroxypropionamides to 2-oxazolidinones uses a NaOBr-mediated Hofmann rearrangement at high temperature,[15] a condition that is too strong for many labile functional groups that are often present in the diverse substrates used in combinatorial chemistry.

In conclusion, the BTI-mediated Hofmann rearrangement proved to be a remarkable method for the synthesis of 2-oxazolidinones. This method is superior to earlier conditions in terms of the yield of product, the cleanness of reaction, and the ease of purification. More importantly, this condition can be easily adapted to the solution- and solid-phase construction of combinatorial libraries of 2-oxazolidinones.

Acknowledgements

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9. For compound **3**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.07 (d, $J=8.1$ Hz, 1H), 7.31–7.19 (m, 4H), 5.38–5.30 (m, 1H), 4.78 (d, $J=4.1$ Hz, 1H), 4.39–4.35 (m, 1H), 4.06–3.99 (m, 2H), 2.97–2.92 (m, 2H), 2.05–1.94 (m, 2H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 171.5, 156.4, 154.5, 136.8, 129.9, 129.0, 127.4, 81.8, 63.8, 56.2, 55.4, 39.2, 28.8. LC-MS (ESI): 364.07 $[MH]^+$, 396.42 [M+MeOH+1]$^+$, 727.37 $[2M+1]^+$.
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11. Ethyl acetate/hexanes was used as the eluting solvent to purify compounds **9**–**11**, while the purification of compound **3** was performed using chloroform/methanol.
12. Spectroscopic data: compound **9**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.30 (br s, 1H), 4.61–4.52 (m, 1H), 3.73 (dd, $J=6.2$, 5.9 Hz, 1H), 2.02–1.24 (m, 8H). ^{13}C NMR (200 MHz, $CDCl_3$): δ ppm 161.4, 76.5, 52.2, 29.0, 27.2, 20.2, 19.9; LC-MS (ESI) 142.0 $[M+1]^+$. Compound **10**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.30 (br s, 1H), 3.82 (dt, $J=11.3$, 3.7 Hz, 1H), 3.26 (dt, $J=10.9$, 3.3 Hz, 1H), 2.15–1.99 (m, 2H), 1.83–1.29 (m, 6H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 161.9, 84.4, 61.3, 29.5, 28.9, 24.2, 23.9; LC-MS (ESI) 142.1 $[M+1]^+$. Compound **11**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.80 (br s, 1H), 4.98 (t, $J=6.5$ Hz, 1H), 4.21 (t, $J=6.6$ Hz, 1H), 2.05–1.97 (m, 1H), 1.78–1.46 (m, 5H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 161.2, 82.9, 57.4, 34.9, 34.3, 22.4; LC-MS (ESI) 128.2 $[M+1]^+$.
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