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AN ASYMMETRIC SYNTHESIS OF 3-ARYL-1,4-OXAZIN-2-ONES: SYNTHESIS OF A KEY INTERMEDIATE OF AN NK_1 RECEPTOR ANTAGONIST†

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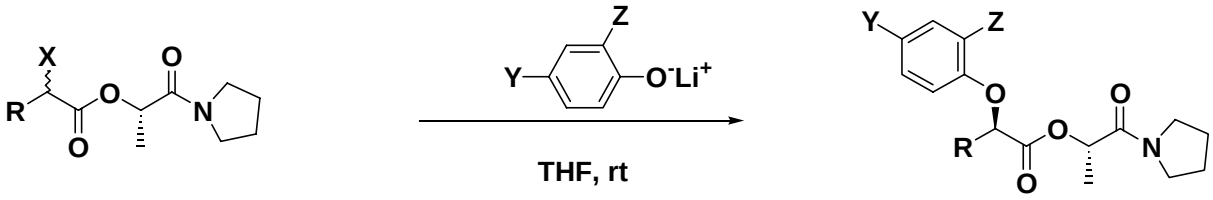
Abstract-Pyrrolidine derived (S)-lactamide auxiliaries mediate a highly diastereoselective coupling reaction between racemic α-halo acids and N-benzylethanolamine. The adducts are readily cyclized upon treatment with a catalytic amount of TsOH giving the above titled compounds in >90% ee. The 4-fluorophenyl substituted oxazinone thus formed is the key intermediate in the synthesis of a potent NK_1 receptor antagonist.

†This paper is dedicated to Professor A. I. Meyers on the occasion of his 70th birthday.

Oxazinones have proven to be quite versatile intermediates in organic synthesis and as such, several syntheses have appeared.[1] Oxazinones have been utilized as chiral auxiliaries in the synthesis of proteinogenic amino acids as well as precursors in the synthesis of highly substituted oxazines.[2] General syntheses of these compounds in optically pure form remain a challenging endeavor. In particular, we were interested in a general and versatile synthesis of 1,4-oxazin-2-ones asymmetrically substituted in the 3-position for study in our NK_1 receptor antagonist program. These compounds have been synthesized from reaction of N-protected amino acids with dibromoethane.[3] They have also been synthesized in a two step process from homochiral α-hydroxy esters through conversion to the triflate followed by displacement with aminoethanol.[4] These routes suffer from low to moderate yields and are limited by the lack of diversity of commercially available amino acids and α-hydroxy esters. Herein we wish to report a general asymmetric synthesis of 3-aryl-1,4-oxazin-2-ones from arylacetic acids. Chirality is derived from a readily available auxiliary and the oxazinones are typically obtained with enantiomeric excesses of 90%. Recently, we described a highly stereoselective coupling reaction between racemic α-halo acids and aryl oxides mediated by a pyrrolidine derived (S)-lactamide auxiliary (Scheme **1**).[5]

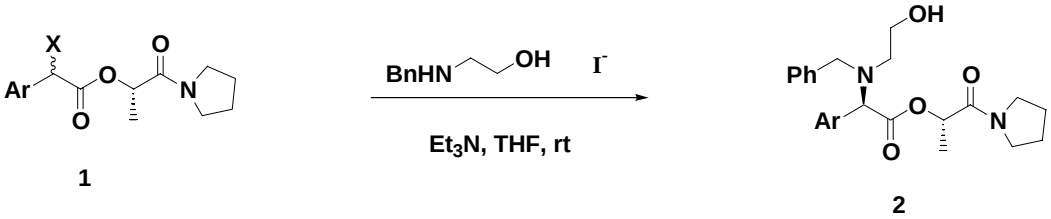
The auxiliary utilized is inexpensive and easily prepared in multigram quantities. The highly diastereoselective reaction has been utilized in the synthesis of a series of serotonin uptake inhibitors.[6]



Scheme **1**

Extension of the methodology incorporating amines as nucleophiles, in particular, ethanolamine equivalents, has led to the development of a broad and stereoselective synthesis of the titled compounds (Table **1**).[7]

Table 1: Lactamide ester coupling with *N*-benzylethanolamine.



Entry	Ar	I⁻ (mol %)	Solvent	Time (h)	DE*
1	Ph	Bu_4NI (100)	THF	0.5	96
2	Ph	Bu_4NI (10)	THF	0.5	96
3	Ph	Bu_4NI (2)	THF	2	90
4	Ph	-	THF	24	62
5	Ph	Bu_4NBr (10)	THF	1.5	94
6	Ph	-	DMF	0.5	92
7	4-F-C_6H_4	Bu_4NI (10)	THF	0.5	97
8	4-F- C_6H_4	-	THF	24	57
9	4-NO_2- C_6H_4	Bu_4NI (10)	THF	0.5	85
10	4-NO_2- C_6H_4	Bu_4NI (10)	THF	1	76
11	3,4-(OCH_2O)-C_6H_4	Bu_4NI (10)	THF	0.5	95

*Diastereoselectivities determined *via* HPLC utilizing a Zorbax Rx-C_8 column and *via* 300 MHz ^{1}H NMR integration of the diastereomeric methyl doublets.

The lactamide esters (**1**) of the racemic α-halo acids were prepared *via* DCC coupling with the commercially available acid. In cases where the α-halo acids were not available, the arylacetic acids

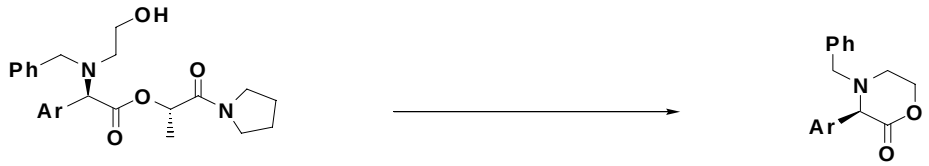
were brominated according to literature procedure.[8] The coupling reaction was conducted by adding *N*-benzylethanolamine to a solution of lactamide ester, triethylamine and an iodide source at ambient temperature. The yields of the coupling reactions ranged from 84-90%.[9] The function of the iodide is to promote a halide to halide transposition reaction which serves to interconvert the two diastereomeric halides. This event is most efficiently brought about with amounts of iodide ranging 10-100 mol%. Lesser amounts lead to slight decreases in stereoselection and rate (Entries **1**-**3**). The absence of extraneous iodide leads to significant rate retardation as well as erosion of diastereoselectivity (Entries **2** and **4**). This is in contrast to results previously reported utilizing lithium phenoxides as nucleophiles.[5] We hypothesized that this was caused by the low solubility of $Et_3NH^+Br^-$ in THF. The lack of extraneous halide in solution would inhibit the transposition reaction thereby decreasing diastereoselection. The theory confirmed by conducting the reaction with 10 mol% of the more soluble tetrabutylammonium bromide (Entry **5**). A diastereoselectivity of 94% was obtained although the reaction was slower than those in which iodide was employed. Conducting the reaction in DMF, a solvent in which $Et_3NH^+Br^-$ is soluble, also led to a high degree of diastereoselection (Entry **6**). The method is tolerant of a variety of substitution about the arene (Entries **7**-**11**). The lowest diastereoselectivities were obtained with the *p*-nitrophenyl derivative (Entry **10**). It was found that the product racemizes under the reaction conditions such that aging the reaction for an additional 0.5 h leads to a 9% decrease in stereoselection.

The amine adducts were then converted to their respective oxazinones upon treatment with a catalytic amount of acid or base (Table **2**).[10] Some loss of stereochemical integrity was observed in all cases. Optimal results were obtained utilizing 20 mol% of *p*-toluenesulfonic acid in toluene at 80 ^oC (Entry **2**). The product was isolated in 82% yield with an enantiomeric excess of 91%. Employing a stoichiometric amount of TsOH leads to a faster reaction rate, but slightly diminished enantiomeric excess (Entry **1**). Decreasing reaction temperature lowered the rate of the reaction but has no effect on stereoselectivity (Entry **4**). Alternative acids have been used with mixed results. Utilization of acetic acid led to a 30% reduction in stereoselectivity (Entry **5**). Boron trifluoride etherate gives an enantiomeric excess of 91% but rate of reaction is slower when compared to those conducted with TsOH. Amino ester (**2**) is instantaneously cyclized to the oxazinone upon addition of a strong base (Entry **8**). The reaction is conducted at –70 ^oC and an enantiomeric excess of 86% is obtained. Running the reaction at ambient temperatures leads to complete epimerization. Milder bases such as cesium carbonate give greatly diminished enantiomeric excesses (Entry **9**). The optimal cyclization conditions were applied to the other analogs with similar results with the exception being the *p*-nitrophenyl derivative.

Treatment of the amino ester with *p*-TsOH results in rapid cyclization to the oxazinone but with total loss of stereochemistry.

The 3-(4-fluorophenyl)-1,4-oxazin-2-one is of particular interest because it is the key intermediate in the

Table 2: Cyclization of amino esters to form oxazinones



2 3

Entry	Ar	Catalyst (Mol%)	Solvent	Temp (^{o}C)	Time (h)	DE	EE*
1	Ph	*p*-TsOH (100)	Tol	80	0.5	96	86
2	Ph	*p*-TsOH (20)	Tol	80	1	96	91
3	Ph	*p*-TsOH (2)	Tol	80	40	96	87
4	Ph	*p*-TsOH (20)	Tol	60	4	96	90
5	Ph	AcOH (20)	Tol	80	24	96	66
6	Ph	HCl (20)	Tol	80	2	96	86
7	Ph	BF_3-OEt_2 (20)	Tol	80	5	96	91
8	Ph	$(TMS)_2NLi$ (10)	THF	-70	0.1	96	86
9	Ph	Cs_2CO_3 (10)	THF	22	1	96	21
10	4-F- C_6H_4	*p*-TsOH (20)	Tol	80	0.5	97	91
11	4-NO_2- C_6H_4	*p*-TsOH (20)	Tol	80	0.5	85	0
12	3,4-(OCH_2O)-C_6H_4	*p*-TsOH (20)	Tol	80	1.5	95	89

*Enantioselectivities determined *via* supercritical fluid chromatography utilizing a Chiracel OJ column

synthesis of a potent substance P NK_1 receptor antagonist.[11] The intermediate has been synthesized from (S)-4-fluorophenylglycine in a two step process. The amino acid is not readily available in bulk and reported syntheses are laborious. An elegant crystallization induced asymmetric transformation has been reported but it is not without issue.[12] The process requires 48 h to be completed and the racemization-resolution reagent, (1S)-3-bromocamphor-8-sulfonic acid, is difficult to obtain at scale. The synthesis reported herein is accomplished in a high yielding 5-step procedure from 4-fluorophenylacetic acid. The process is quite general and does not rely on the availability of the corresponding amino acids.

In conclusion, a general and versatile asymmetric synthesis of 3-aryl-1,4-oxazin-2-ones is reported. The chirality is derived from a readily available and inexpensive lactamide auxiliary and enantiomeric excesses are typically 90%. An efficient high yielding synthesis of the key intermediate of a substance P NK_1 receptor antagonist has been developed.

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9. The following procedure from Table **1**, Entry **2** is typical: To a solution of α-bromo ester (4 g, 11.8 mmol) , *N*-benzylethanolamine (1.3 mL, 13 mmol) and Bu_4NI (0.4 g, 1.2 mmol) in THF (40 mL) was added Et_3N (1.8 mL, 12.9 mmol). The reaction was aged 0.5 h and partitioned between 1 N HCl and MTBE. The aqueous phase was basified with $NaHCO_3$ (5%) and was extracted 2 x MTBE. The combined organic phases were dried (Na_2SO_4), concentrated and purified via flash chromatography to yield 4.1 g (84%) of product as a viscous oil.
10. The following procedure from Table **2**, Entry **2** is typical: To a solution of amino ester (0.31 g, 0.76 mmol) in toluene (4 mL) was added *p*-TsOH (27 mg, 0.14 mmol). The reaction was heated at 80 ^oC for 1 h, cooled and washed with $NaHCO_3$ (5%) followed by brine. The reaction was concentrated and purified via flash chromatography to give 0.18 g of oxazinone as a colorless solid.
11. For the synthesis of this and other substance P NK_1 receptor antagonists see: (a) J. J. Hale, S. G. Mills, M. MacCoss, S. K. Shah, H. Qi, D. J. Mathre, M. A. Cascieri, S. Sadowski, C. D. Strader, D. E. MacIntyre, and J. M. Metzger, *J. Med. Chem*., 1996, **39**, 1760. (b) J. J. Hale, S. G. Mills, M. MacCoss, P. E. Finke, M. A. Cascieri, S. Sadowski, E. Ber, G. G. Chicchi, M. Kurtz, J. Metzger, G. Eiermann, N. N. Tsou, F. D. Tatersall, M. N. J. Rupniak, A. R. Williams, W. Rycroft, R. Hargreaves, and D. E. MacIntyre, *J. Med. Chem*., 1998, **41**, 4607. (c) C. J. Cowden, R. D. Wilson, B. C. Bishop, I. F. Cottrell, A. J. Davies, and U. -H. Dolling, *Tetrahedron Lett*., 2000, **41**, 8661. (d) D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U. -H. Dolling, and P. J. Reider, *Org. Lett*., 2001, **3**, 671.
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