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Enantiospecific Synthesis of 6-Substituted N-Aryl-1,3-Oxazin-2-Ones

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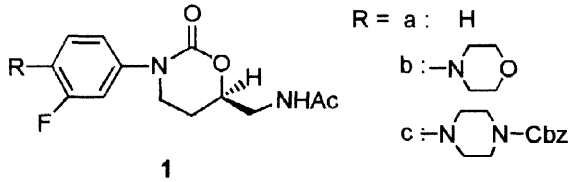
Abstract:

A novel and facile synthesis of 6-substituted chiral N-aryl-1,3-oxazin-2-one derivatives has been achieved starting from readily available (*S*)-aspartic acid.

Keywords : Enantiospecificity; regioselective; carbamates; oxazines.

The cyclic carbamate oxazinone is an important 6-membered heterocyclic ring system which is present in many biologically important natural products like maystansine, maystanprine, maytanbutine and colubrinol.[1] In addition, oxazinone derivatives are known to exhibit a variety of biological activities such as antiulcer,[2a] anticonvulsant,[2b] penetration enhancer,[2c] sedative,[2d] analgesic,[2e] vasodilator,[2e] hypertensive[2e] and antidepressant.[2d] 1,3-Oxazin-2-one derivatives have also been used as key intermediates in the synthesis of several natural products such as (+)-negamycin[3], L-ristosamine[4], and L-daunosamine[4] as well as in the synthesis of 1,3-*syn* aminoalcohols.[5] Recently, oxazinones have been recognized as chiral auxiliaries[6] in asymmetric synthesis.



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In our pursuit to develop oxazinone derivatives as useful and new therapeutic agents, we gained interest in the synthesis of chiral 6-substituted N-aryl-1,3-oxazin-2-one **1**. Although several methods[7] are available for the synthesis of simple oxazinones, no procedure was found to be suitable for the chiral synthesis of **1**. In this communication, we reveal our efforts towards the synthesis of chiral oxazinones **1**. The synthetic strategy is outlined in scheme-1. Following the known procedure,[8] epoxy-tosylate **2** was readily prepared starting from (*S*)-aspartic acid. Selective alkylation by **2** with N-carbobenzyloxy-3-fluoro-4-substituted aniline was best achieved using sodium hydride in DMSO at *ca* 25 °C to furnish epoxy-carbamate **3** in 63-70% yields. The

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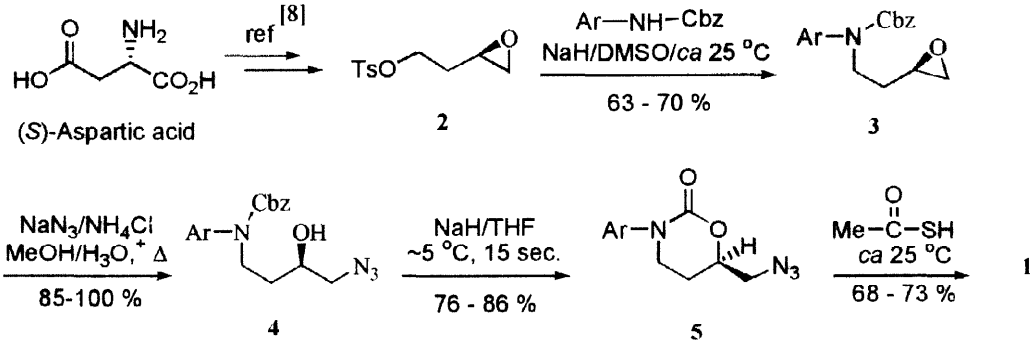
regioselective ring opening of epoxide **3** with sodium azide was realized using ammonium chloride[9] as a catalyst (85-100%). After a number of failures, we achieved the cyclization of hydroxy azide **4** using sodium hydride in THF at 5 °C for 15 sec. to furnish the oxazinone **5** in 76-86 % yields. It is pertinent to mention that the reaction temperature and time are very crucial for the success of this reaction. The reaction was found to be very sluggish at lower temperature but longer reaction time and higher temperature resulted in the isolation of ring cleaved products. Finally, reaction of azide **5** with thioacetic acid[10] at room temperature gave the target compound **1** in 68-73% yields.[11]



Scheme-1

In conclusion, we have developed a novel and simple route for the synthesis of substituted chiral 1,3-oxazin-2-ones, which will find application in organic synthesis.

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[11] Physical data: **1a**) mp 128-130 °C; $[\alpha]_D^{25}$ = -94.3 (c = 1, $CHCl_3$); IR (KBr): 3266, 3065, 2956, 1690, 1671, 1631, 1550, 1488, 1436, 1186, 699 cm^{-1}; ^1H NMR($CDCl_3$) : δ 7.42-7.30 (m, 1H); 7.18-6.92 (m, 3H); 6.16 (bs, 1H); 4.58- 4.45 (m, 1H); 3.85-3.60 (m, 3H), 3.45-3.28 (m, 1H), 2.23-1.99 (m, 2H), 2.03 (s, 3H). **1b**) mp 169-170 °C; $[\alpha]_D^{25}$ = -85.5 (c = 1, $CHCl_3$); IR (KBr): 3324, 3074, 2863, 1692, 1635, 1546, 1519, 1443, 1113, 817, 599 cm^{-1}; ^1H NMR($CDCl_3$) : δ 7.09-6.86 (m, 3H), 6.13 (bs, 1H), 4.58-4.47 (m, 1H), 3.86 (t, 4H, J = 4.6 Hz), 3.81-3.55 (m, 3H), 3.45-3.30 (m, 1H), 3.08 (t, 4H, J= 4.8 Hz), 2.15-1.99 (m, 2H), 2.04 (s, 3H). Mass (m/z): 351 (M^+, 10%). **1c**) mp 191-193 °C; $[\alpha]_D^{25}$ = -63.9 (c =1, $CHCl_3$); IR (KBr): 3440, 3291, 2926, 1685, 1653, 1515, 1432, 1243, 1128, 1073, 696 cm^{-1}; ^1H NMR($CDCl_3$) δ: 7.37 (s, 5H), 7.08-6.92 (m, 3H), 6.13 (bs, 1H), 5.16 (s, 2H), 4.52-4.43 (m, 1H), 3.78-3.58 (m, 7H), 3.39-3.25 (m, 1H), 3.03 (bs, 4H), 2.20-1.95 (m, 2H), 2.03 (s, 3H); Mass (m/z): 484(M^+, 3%), 440 (70%), 368 (30%), 340 (12%), 264 (20%), 206 (5%), 177 (10%), 91 (100%).