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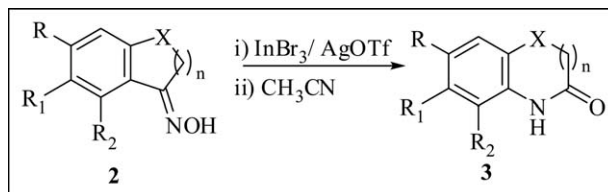
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Beckmann rearrangement of (*E*)-4-chromanone oxime, (*E*)-5-oximino-3,4-dihydro-1(2*H*)-benzoxepines, and (*E*)-5-oximino-3,4-dihydro-1(2*H*)-benzothiepine are catalyzed by InBr₃ and AgOTf in refluxing acetonitrile resulting in the formation of pharmaceutically active heterocycles benzoxazepin-4-one, 5-oxo-benzoxazocines, and 5-oxo-benzothiazocine derivative, respectively, in excellent yield.

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INTRODUCTION

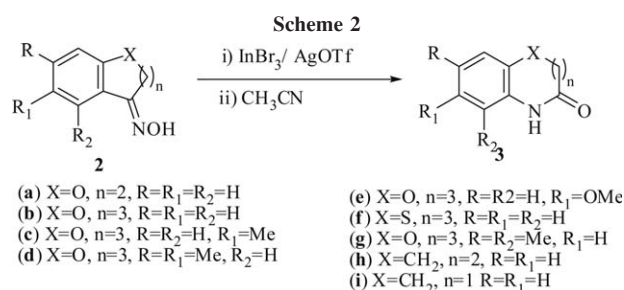
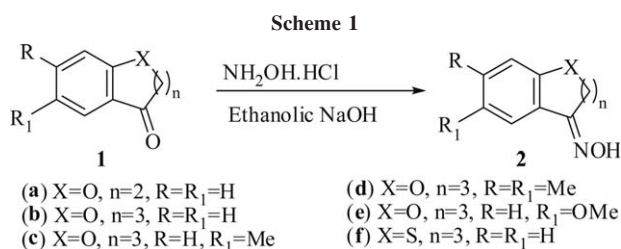
Beckmann rearrangement involving the transformation of ketoximes into amides is a fundamental reaction in organic synthesis and has led to numerous applications due to the ease with which nitrogen can be inserted into carbon chains starting from prepared ketones [1]. Generally, strong Bronstead/Lewis acids ranging from stoichiometric to catalytic amounts are used to accomplish the Beckmann rearrangement. Development of this important rearrangement promoted by a catalytic amount of active species has been strongly desired during the last decade. In recent years, new reagents such as BF₃·Et₂O [2], super critical water [3], and metaboric acid [4] have been deployed for the synthesis of lactams by Beckmann rearrangement. Ketoximes undergo Beckmann rearrangement by use of chlorosulphonic acid in presence of toluene with high selectivity [5]. Yang and coworkers have reported Beckmann rearrangement of ketoximes by use of an effective and green catalyst, sulfamic acid [6]. Ketoximes undergo Beckmann rearrangement under very mild condition in presence of 2,4,6-trichloro[1,3,5]-triazene in DMF at room temperature to form amides [7]. Silica-supported MoO₃ has been used as a catalyst for the Beckmann rearrangement of oximes into amides [8]. Zhu *et al.* have used BOP-Cl(*tris*(2-oxo-3-oxazolidinyl)phosphinic chloride, the first organophosphorous catalyst, for the conversion of ketoximes into amides by Beckmann rearrangement [9]. Dai and coworkers have used Grignard reagent for the first time to induce Beckmann rearrangement directly without any additional protic agents for the synthesis of 2-aryl-1-benzazocines [10].

RESULTS AND DISCUSSION

As part of our research program to study indium bromide and silver triflate for synthesis of different industrially and biologically important heterocycles [11] and indium chloride [12] catalyzed Beckmann rearrangement of α -tetralone oxime, we became interested in the synthesis of analogs of oxazine and oxazepine [11].

We have studied indium bromide, a economical catalyst better than indium chloride and silver triflate combination of reagents, for the synthesis of 2,3-dihydrobenzo[*b*][1,4]oxazepin-4(5*H*)-one (**3a**), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazocin-5(6*H*)-ones (**3b–e**), and 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazocin-5(6*H*)-one (**3f**) from corresponding oximes (**2a–f**), [13], which is more stable stereoisomer than *Z*-oximes [14]. The (*E*)-oximes **2** used for the Beckmann rearrangement were synthesized from corresponding ketones by reaction with NH₂OH·HCl in ethanolic NaOH (Scheme 1) [15]. The oximes were characterized by their IR, ¹H NMR, and elemental analytical data (Table 1). (*E*)-5-oximino-3,4-dihydro-1(2*H*)-benzoxepin (**2b**; X = O, *n* = 3, R₁=R₂=H) in IR spectrum exhibited OH band at 3244 cm^{−1}. In ¹H NMR spectra, a multiplet for two protons at C-3 appeared at δ 2.00; a multiplet at δ 2.85 appeared for 4-CH₂; a triplet for OCH₂ appeared at δ 4.25; a multiplet at δ 7.6 appeared for 4-phenyl-H. The elemental analytical data for C, H, and N obtained for **2b** were within ± 0.25 range.

Our efforts to study Beckmann rearrangement of (*E*)-oximes **2** using InBr₃ resulted in very poor yield of lactam **3** (5–15%). However, we were successful in carrying out Beckmann rearrangement of (*E*)-oximes **2**



derived from cyclic ketones **1** with InBr₃ and AgOTf in good to excellent yield (Scheme 2).

Thus, the reaction of (*E*)-oxime derivatives **2** on reaction with a mixture of InBr₃ and AgOTf as catalyst

resulted in the formation of rearranged cyclic amide 2,3-dihydrobenzo[*b*][1,4]oxazepin-4(5*H*)-one (**3a**), 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazocin-5(6*H*)-ones (**3b-e**), 3,4-

Table 1
Physical and spectral data of heterocyclic (*E*)-oximes **2a-f** [15].

2	Compound	Yields	Mp (°C)	Physical/spectral data
a		81%	140	(<i>E</i>)-4-Chromanone oxime (2a): Colorless solid; crystallized from aq. EtOH; colorless crystals [16].
b		86%	94	(<i>E</i>)-5-Oximino-3,4-dihydro-1(2 <i>H</i>)-benzoxepine (2b): Colorless solid; crystallized from aq. EtOH; colorless crystals [17]; IR (KBr): 512, 656, 750, 826, 972, 1050, 1126, 1203, 1285, 1491, 1606, 2367, 2952, 3244 cm ⁻¹ ; ¹ H NMR: δ 2.00 (m, 2H, 3-CH ₂), 2.85 (m, 2H, 4-CH ₂), 4.25 (t, 2H, OCH ₂), 7.6 (m, 4H, phenyl-H); Anal. Calcd. for C ₁₀ H ₁₁ NO ₂ (177): C, 67.78; H, 6.26; N, 7.90; Found: C, 67.58; H, 6.22; N, 7.86.
c		84%	73	(<i>E</i>)-7-Methyl-5-oximino-3,4-dihydro-1(2 <i>H</i>)-benzoxepine (2c): Crystallized from benzene-Hexane; pale yellow crystals [18]; IR (KBr): 461, 511, 587, 655, 748, 825, 859, 886, 959, 1055, 1079, 1125, 1202, 1236, 1284, 1320, 1378, 1412, 1454, 1491, 1605, 2363, 2952, 3244 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.79 (bh, 1H, OH), 2.01 (m, 2H, CH ₂), 2.31 (s, 3H, CH ₃), 2.92 (t, 2H, CH ₂), 4.14 (t, 2H, OCH ₂), 6.88 (d, 1H, phenyl-H), 7.08 (m, 1H, phenyl-H), 7.28 (d, 1H, phenyl-H); Anal. Calcd. for C ₁₁ H ₁₃ NO ₂ (191): C, 69.09; H, 6.85; N, 7.32; Found: C, 68.79; H, 6.75; N, 7.21.
d		88%	110	(<i>E</i>)-7,8-Dimethyl-5-oximino-3,4-dihydro-1(2 <i>H</i>)-benzoxepine (2d): Crystallized from benzene-Hexane; dark yellow crystals [19].
e		85%	86	(<i>E</i>)-7-Methoxy-5-oximino-3,4-dihydro-1(2 <i>H</i>)-benzoxepine (2e): Crystallized from benzene-Hexane; pale yellow crystals [20]; IR (KBr): 512, 588, 749, 826, 969, 1056, 1205, 1283, 1380, 1492, 1606, 2953, 3230 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.80 (m, 2H, CH ₂), 2.82 (m, 2H, CH ₂), 3.68 (s, 3H, OCH ₃), 3.98 (t, 2H, CH ₂), 6.85 (m, 3H, phenyl-H); Anal. Calcd. for C ₁₁ H ₁₃ NO ₃ (207): C, 63.76; H, 6.32; N, 6.76; Found: C, 63.64; H, 6.29; N, 6.73.
f		87%	98	(<i>E</i>)-5-Oximino-3,4-dihydro-1(2 <i>H</i>)-benzothiepine (2f): Crystallized from benzene-Hexane; brown crystals [21]; IR (KBr): 466, 539, 634, 754, 904, 960, 8035, 1087, 1150, 1244, 1300, 1351, 1440, 1586, 1628, 1721, 1853, 2368, 2923, 3062, 3250 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 2.16 (m, 2H, CH ₂), 2.89–3.01 (m, 4H, CH ₂), 7.17–7.51 (m, 4H, phenyl-H), 8.63 (bh, 1H, OH); Anal. Calcd. for C ₁₀ H ₁₁ NOS (193): C, 62.15; H, 5.74; N, 7.25; S, 16.59; Found: C, 61.86; H, 5.71; N, 7.23; S, 16.55.

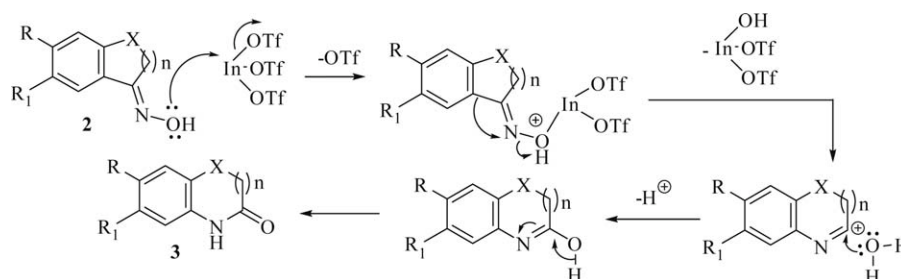
Table 2

Physical and spectral data of lactam **3a-i** synthesized by Beckmann rearrangement of heterocyclic (*E*)-oxime **2** [22].^a

3	Compound	Yields	Mp (°C)	Physical/spectral data
a		85%	124–126	2,3-Dihydro-1,5-Benzoxazepin-4-one (3a): Colorless solid; crystallized with CHCl ₃ /Hexane [23]; IR (KBr): 571, 646, 684, 720, 840, 948, 1034, 1067, 1099, 1173, 1218, 1231, 1284, 1350, 1399, 1432, 1441, 1591, 1653, 2950, 3051, 3176, 3283, 3421 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.80 (bs, 1H, NH), 2.72 (t, 2H, <i>J</i> = 6 Hz, CH ₂), 4.25 (t, 2H, <i>J</i> = 6 Hz, OCH ₂), 7.00–7.09 (m, 3H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 37, 70, 115, 120, 121, 127, 128, 154, 172; Anal. Calcd. for C ₉ H ₉ NO ₂ (163): C, 66.25; H, 5.56; N, 8.58; Found: C, 66.04; H, 5.52; N, 8.51.
b		81%	148	5-Oxo-2,3,4,5-tetrahydro-6H-1,6-benzoxazocine (3b): Colorless solid; crystallized from benzene, colorless crystals [17]; IR (KBr): 586, 635, 673, 764, 807, 870, 897, 934, 1004, 1058, 1090, 1183, 1208, 1241, 1285, 1352, 1399, 1439, 1438, 1597, 1663, 2957, 3186, 3292, 3428 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.76 (bs, 1H, NH), 2.03 (m, 2H, CH ₂), 2.37 (t, 2H, <i>J</i> = 6 Hz, OCH ₂), 4.26 (t, 2H, <i>J</i> = 6 Hz, CH ₂), 7.09–7.26 (m, 3H, phenyl-H), 7.69 (m, 1H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 26, 31, 75, 115, 120, 121, 127, 129, 155, 173; Anal. Calcd. for C ₁₀ H ₁₁ NO ₂ (177): C, 67.78; H, 6.26; N, 7.90; Found: C, 67.69; H, 6.23; N, 7.84.
c		75%	141	5-Oxo-8-methyl-2,3,4,5-tetrahydro-6H-1,6-benzoxazocine (3c): Colorless solid; crystallized from benzene [17]; IR (KBr): 670, 773, 816, 871, 897, 935, 1008, 1056, 1080, 1126, 1166, 1190, 1222, 1290, 1318, 1352, 1394, 1442, 1509, 1591, 1667, 2364, 2945, 3230, 3423 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.89 (bs, 1H, NH), 2.01 (m, 2H, CH ₂), 2.25 (s, 3H, CH ₃), 2.36 (m, 2H, CH ₂), 4.19 (t, 2H, <i>J</i> = 6 Hz, OCH ₂), 6.91 (s, 1H, phenyl-H), 7.03 (s, 1H, phenyl-H), 7.96 (s, 1H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 21, 26, 31, 75, 115, 120, 127, 128, 135, 155, 176; Anal. Calcd. for C ₁₁ H ₁₃ NO ₂ (191): C, 69.09; H, 6.85; N, 7.32; Found: C, 68.88; H, 6.81; N, 7.29.
d		88%	194	5-Oxo-8,9-dimethyl-2,3,4,5-tetrahydro-6H-1,6-benzoxazocine (3d): Colorless solid; crystallized from Hexane, colorless crystals [24]; IR (KBr): 468, 563, 680, 768, 819, 890, 1000, 1071, 1150, 1246, 1313, 1396, 1442, 1656, 3043, 3174 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.71 (s, 1H, NH), 2.02 (m, 2H, CH ₂), 2.24 (s, 3H, CH ₃), 2.26 (s, 3H, CH ₃), 2.32 (m, 2H, CH ₂), 4.19 (t, 2H, <i>J</i> = 6 Hz, OCH ₂), 7.05 (s, 1H, phenyl-H), 7.35 (s, 1H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 19, 20, 26, 31, 75, 120, 123, 124, 132, 139, 148, 176; Anal. Calcd. for C ₁₂ H ₁₅ NO ₂ (205): C, 70.22; H, 7.37; N, 6.82; Found: C, 69.98; H, 7.34; N, 6.78.
e		84%	135	5-Oxo-8-methoxy-2,3,4,5-tetrahydro-6H-1,6-benzoxazocine (3e): Colorless solid, crystallized from CHCl ₃ /Hexane; colorless crystals; IR (KBr): 564, 613, 675, 718, 774, 811, 863, 932, 1011, 1037, 1059, 1088, 1186, 1210, 1247, 1286, 1312, 1352, 1402, 1440, 1458, 1508, 1595, 1670, 2366, 2957, 3240, 3429 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.62 (s, 1H, NH exchangeable with D ₂ O shake), 2.01 (m, 2H, CH ₂), 2.37 (t, 2H, <i>J</i> = 6 Hz, CH ₂), 3.78 (s, 3H, OCH ₃), 4.16 (t, 2H, <i>J</i> = 6 Hz, OCH ₂), 6.59 (d, 1H, phenyl-H), 6.80 (m, 2H, phenyl-H), 7.09 (d, 1H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 26, 31, 55, 75, 110, 114, 115, 127, 150, 155, 176; Anal. Calcd. for C ₁₁ H ₁₃ NO ₃ (207): C, 63.76; H, 6.32; N, 6.76; Found: C, 63.58; H, 6.28; N, 6.71.
f		86%	176	5-Oxo-2,3,4,5-tetrahydro-6H-1,6-benzothiazocine (3f): Brown color solid; crystallized from Hexane; brown crystals [25]; IR (KBr): 487, 517, 557, 628, 694, 753, 875, 954, 1026, 1136, 1185, 1235, 1314, 1333, 1444, 1472, 1586, 1661, 2365, 2930, 3046, 3172 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.25 (s, 1H, NH), 1.88 (m, 2H, CH ₂), 2.15 (m, 2H, CH ₂), 2.84 (m, 2H, SCH ₂), 7.07–7.81 (m, 4H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 28, 32, 34, 125, 126, 131, 132 (2C), 148, 172; Anal. Calcd. for C ₁₀ H ₁₁ NOS (193): C, 62.15; H, 5.74; N, 7.25; S, 16.59; Found: C, 61.92; H, 5.71; N, 7.22; S, 16.54.
g		80%	212	5-Oxo-7,9-dimethyl-2,3,4,5-tetrahydro-6H-1,6-benzoxazocine (3g): Colorless solid; crystallized from Hexane; colorless crystals [26]; IR (KBr): 467, 512, 563, 601, 625, 679, 767, 819, 889, 1000, 1070, 1149, 1182, 1245, 1271, 1313, 1396, 1442, 1495, 1657, 2368, 2954, 3043, 3174 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.71 (s, 1H, NH), 2.04 (m, 2H, CH ₂), 2.24 (s, 3H, CH ₃), 2.29 (s, 3H, CH ₃), 2.32 (m, 2H, CH ₂), 4.19 (m, 2H, OCH ₂), 6.81 (d, 2H, phenyl-H); ¹³ C NMR (CDCl ₃): δ 18, 20, 26, 31, 75, 121, 126, 127, 133, 137, 155, 176; MS (m/z): 206 (M ⁺ +1); Anal. Calcd. for C ₁₂ H ₁₅ NO ₂ (205): C, 70.22; H, 7.37; N, 6.82; Found: C, 70.10; H, 7.33; N, 6.79.
h		89%	141	4,5-dihydro-1H-benzob[blazepin-2(3H)-one (3h): Colorless solid; crystallized from CHCl ₃ /Hexane; colorless crystals [27]; IR (KBr): 595, 632, 682, 763, 786, 817, 863, 915, 946, 980, 1020, 1054, 1110, 1156, 1254, 1292, 1327, 1385, 1439, 1490, 1600, 1664, 2365, 2866, 2930, 2975, 3062, 3192 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.84 (s, 1H, NH), 2.25 (m, 2H, CH ₂), 2.38 (t, 2H, <i>J</i> = 7 Hz, CH ₂), 2.83 (t, 2H, <i>J</i> = 7 Hz, CH ₂), 7.00–7.28 (m, 4H, phenyl-H), 8.13 (bs, 1H, N=C-OH); ¹³ C NMR (CDCl ₃): δ 22, 35, 38, 126 (2C), 127, 128, 136 (2C), 172; Anal. Calcd. for C ₁₀ H ₁₁ NO (161): C, 74.51; H, 6.88; N, 8.69; Found: C, 74.48; H, 6.82; N, 8.60.
i		87%	166	3,4-dihydroquinolin-2(1H)-one (3i): Colorless solid; crystallized from Benzene/Hexane; colorless crystals [28]; IR (KBr): 566, 613, 680, 748, 815, 867, 914, 1033, 1114, 1200, 1245, 1281, 1341, 1385, 1434, 1492, 1593, 1684, 1796, 1905, 2366, 2737, 3093, 3195 cm ⁻¹ ; ¹ H NMR (CDCl ₃): δ 1.67 (s, 1H, NH), 2.64 (t, 2H, <i>J</i> = 7 Hz, CH ₂), 2.97 (t, 2H, <i>J</i> = 7 Hz, CH ₂), 6.77–7.26 (m, 4H, phenyl-H), 8.38 (bs, 1H, N=C-OH); ¹³ C NMR (CDCl ₃): δ 26, 30, 120, 125, 126, 128, 136, 137, 171; Anal. Calcd. for C ₉ H ₉ NO (147): C, 73.45; H, 6.16; N, 9.52; Found: C, 73.38; H, 6.12; N, 9.48.

^a Stereo stable configuration of lactam is prepared by Chem 3D ultra 10.

Scheme 3



dihydro-2*H*-benzo[*b*][1,4]thiazocin-5(6*H*)-one (**3f**), 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-one (**3g**), and 3,4-dihydroquinolin-2(1*H*)-one (**3h**) in excellent yields (Scheme 2, Table 2) [22].

Compound **3e** in IR spectrum exhibited C=O band at 1670 cm⁻¹ and NH at 3240 cm⁻¹. In ¹H NMR spectra, a singlet at δ 1.62 exchangeable with D₂O appeared for NH, a multiplet at δ 2.01 for CH₂ appeared for 2-protons at C-4. A triplet at 2.37 for 2-protons of CH₂ appeared for C-3 and a singlet at δ 3.78 for 3-protons appeared for OMe, a triplet at 4.16 for 2-protons of OCH₂ and two doublets and multiplet for aromatic protons appeared between δ 6.59 and 7.09.

The Beckmann rearrangement reaction of (*E*)-keto oximes **2** in presence of InBr₃/AgOTf is regioselective leading to formation of lactam **3** exclusively. This became evident by independent synthesis of lactam **3b** from ketone **1b** [29]. In presence of AgOTf, indium bromide is converted into indium triflate, the triflate ion being a better leaving group than bromide ion increases the rate of the reaction. It is essential to use silver triflate as the triflate anion is weakly coordinating, it is useful as a halide abstraction reagent. The role of Ag⁺ is to facilitate the acceleration of the rate of reaction as AgBr is precipitated as side product.

The plausible mechanism of formation of lactam **3** from (*E*)-ketoxime **2** is exhibited in Scheme 3.

The new route to synthesis of these pharmaceutically active heterocycles and reactivity of other metal triflates are being further explored. In summary, we have demonstrated InBr₃- and AgOTf-catalyzed Beckmann rearrangement of cyclic-(*E*)-oximes **2** resulting in the formation of rearranged cyclic amides **3** in excellent yields.

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