A Facile Synthetic Method for Indolic Enamides

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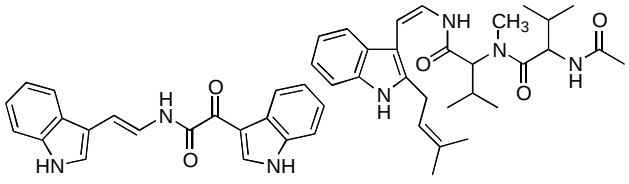
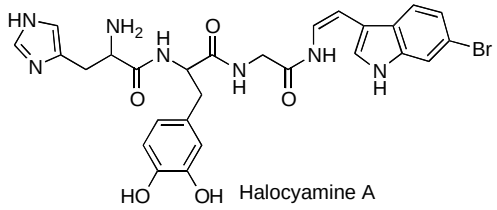
We report a facile method for preparing enamides, based on the Curtius rearrangement and acylation of alkenylcarbamate. Using this approach, a total synthesis of coscinamide B, a bis indolic enamide, was achieved.

We have recently reported the stereoselective synthesis of enamides using Curtius rearrangement and organometallic addition to the isocyanates.[1] Its utility was shown by the construction of side-chain moieties of salicylihalamides, oximidines, lobatamides, CJ-12950 and CJ-13357.[1,2] This methodology was also proved efficient through the recent total syntheses of enamide natural products.[2b,3)]

In conjunction with our synthetic efforts on the synthesis of enamide natural products, we have been interested in indolic enamides (Scheme 1).[4] However our initial approach seemed to have difficulties in synthesizing these natural products. In fact, during the course of our synthetic study on coscinamides, we found our initial approach proved unsuccessful. So we needed to establish methodology suitable for these targets. Herein we report a total synthesis of coscinamide B using newly developed approach.

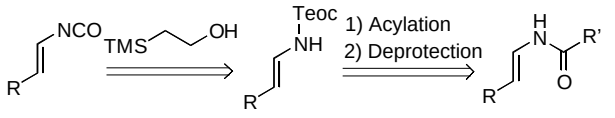




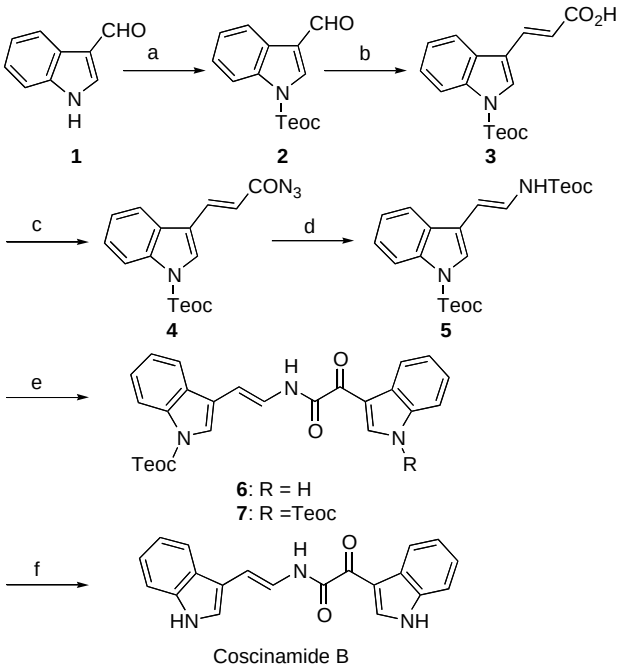
Scheme 1.

Our new plan to construct enamides is outlined in Scheme 2. The alkenyl isocyanate could be trapped with 2-(trimethylsilyl)ethanol to form *N*-[2-(trimethylsilyl)ethoxycarbonyl]-protected (Teoc-protected) enamine. Acylation of this carbamate and deprotection of Teoc group could give the desired enamide.[5] Smith, III and his co-worker have recently reported a total synthesis of (+)-salicylihalamide using this approach.[6]

Indole-3-carbaldehyde (**1**) was first protected as the Teoc-carbamate by using Roush's method to give **2** in 76% yield (Scheme 3).[7] Condensation of **2** with malonic acid in the presence of piperidine provided *N*-Teoc-*trans*-3-indolacrylic acid (**3**).[8]



Scheme 2.



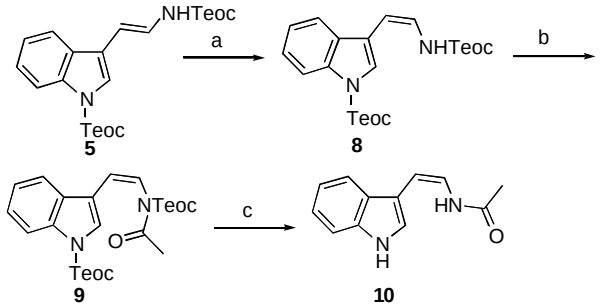
a; Teoc-imid, pyridine, 76%. b; malonic acid, piperidine, pyridine, 94%. c; (1) $ClCO_2Et$, Et_3N, acetone, (2) NaN_3, acetone-H_2O, 88% for 2 steps. d; 100 °C, toluene then 2-(trimethylsilyl)ethanol, 96%, e; NaHMDS, THF then 3-indoleglyoxyl chloride, **6** for 24% and **7** for 24% (32% of recovered **5**). f; TBAF, THF, 92% from **6**, 92% from **7**.

Scheme 3.

Treatment of **3** with $ClCO_2Et$ and Et_3N in acetone, followed by addition of NaN_3 gave the acyl azide (**4**) in 88% yield.[9] After thermal decomposition of the acyl azide, the intermediate isocyanate was trapped with 2-(trimethylsilyl)ethanol to give **5** in 96% yield. With *N*-Teoc-alkenylcarbamate (**5**) in hand, we moved to the acylation step. Treatment of **5** with NaHMDS in THF, followed by addition of 3-indoleglyoxyl chloride gave **6** in 24% yield and **7** in 24% yield.[10] And 32% of **5** was recovered. Although the use of other bases (*n*-BuLi, LiHMDS, NaH, *t*-BuOK, KHMDS, Cs_2CO_3 in the presence of 18-crown-6, DBU, Et_3N, DMAP in pyridine) was investigated, none or only a trace amount of **6** was obtained. Using methyl 3-indoleglyoxalate instead of 3-indoleglyoxyl chloride was also unsuccessful.[11] Deprotection of Teoc group was accomplished by treatment of TBAF to afford coscinamide B. The IR, ^1H and ^{13}C NMR spectral

data were in good accordance with those of natural product.[4a,12)]

Next we attempted to obtain *Z*-enamides. Irradiation of **5** with a high-pressure mercury arc lamp afforded a mixture of *E*- and *Z*-alkenylcarbamate, which were easily separated by silica gel chromatography. Treatment of *Z*-alkenylcarbamate (**8**) with NaHMDS, followed by addition of acetyl chloride gave **9** in 64% yield. And deprotection of Teoc group with TBAF afforded *Z*-enamide (**10**) in 89% yield.



a; hν (high pressure mercury arc lamp), EtOAc, 18% (77% of recovered **5**). b; NaHMDS, THF then AcCl, 64%. c; TBAF, THF, 89%.

Scheme 4.

In summary, we show a total synthesis of coscinsmide B using newly developed approach, which involved acylation of Teoc-protected enamines and deprotection of Teoc group. We believe that this methodology is applied to the preparation of other natural indolic enamides.

This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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10 To a solution of **5** (108 mg, 0.24 mmol) in THF (6 ml) was added a solution of NaHMDS (730 μl, 1 M solution in THF, 0.73 mmol) at 0 °C for 10 min. Then 3-indoleglyoxyl chloride (100 mg, 0.48 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 3 hour. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by PTLC (Hexane : EtOAc = 7 : 1) to yield 28 mg (0.059 mmol, 24%) of **6**, 36 mg (0.058 mmol, 24%) of **7**. And 34 mg (32%) of recovered **5**. **6**: yellow needle, mp 162–164 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.10 (9H, s), 1.23 (2H, m), 4.51 (2H, m), 6.49 (1H, d, J = 14.7 Hz), 7.27–7.54 (5H, m), 7.58 (1H, dd, J = 14.7 Hz, 11.1 Hz), 7.65 (1H, s), 7.77 (1H, dd, J = 6.6 Hz, 0.9 Hz), 8.21 (1H, d, J = 8.4 Hz), 8.44 (1H, m), 8.91 (1H, brs), 9.12 (1H, d, J = 3 Hz), 9.31 (1H, d, J = 11.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ -1.5, 17.8, 65.9, 107.6, 111.7, 113.3, 115.4, 117.4, 119.9, 121.6, 122.5, 122.7, 123.2, 123.6, 124.4, 125.0, 126.6, 128.4, 135.7, 138.4, 150.9, 159.0, 179.4; IR (KBr): 4214, 3263, 3020, 2957, 2398, 1726, 1656, 1627, 1456, 1396, 1248, 1217, 942, 861, 839 cm^{-1}. **7**: yellow solid, mp 159–161 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.10 (9H, s), 0.11 (9H, s) 1.20–1.30 (4H, m), 4.59-4.61 (4H, m), 6.52 (1H, d, J = 15.0 Hz), 7.28–7.34 (2H, m), 7.37–7.46 (2H, m), 7.58 (1H, dd, J = 15.0 Hz, 11.1 Hz), 7.65 (1H, s), 7.78 (1H, d, J = 8.1 Hz) 8.20–8.27 (2H, m), 8.38–8.41 (1H, m), 9.17 (1H, d, J = 11.1 Hz), 9.46 (1H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): δ -1.5, -1.5, 17.8, 17.8, 65.9, 67.2, 108.1, 115.2, 115.5, 115.6, 117.2, 120.0, 121.3, 122.4, 122.9, 123.3, 124.1, 125.0, 125.3, 126.1, 126.4, 127.8, 128.2, 135.2, 138.6, 150.2, 152.1, 157.9, 180.8; IR (KBr): 3352, 2957, 1744, 1685, 1645, 1454, 1396, 1351, 1233, 1098, 1047, 941, 862, 837, 753 cm^{-1}.

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12 Synthetic coscinamide B had $[\alpha]_D$ 0.6 (*c* 0.5, MeOH) [lit.: $[\alpha]_D$ 23.6 (*c* 0.83, MeOH)]. We think natural coscinamide B was contaminated by optically active compound(s).