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A FACILE SYNTHESIS OF 4-(SULFONYLMETHYL)INDOLES FROM 4-OXO-4,5,6,7-TETRAHYDROINDOLE: FORMAL TOTAL SYNTHESIS OF 6,7-SECOAGROCLAVINE

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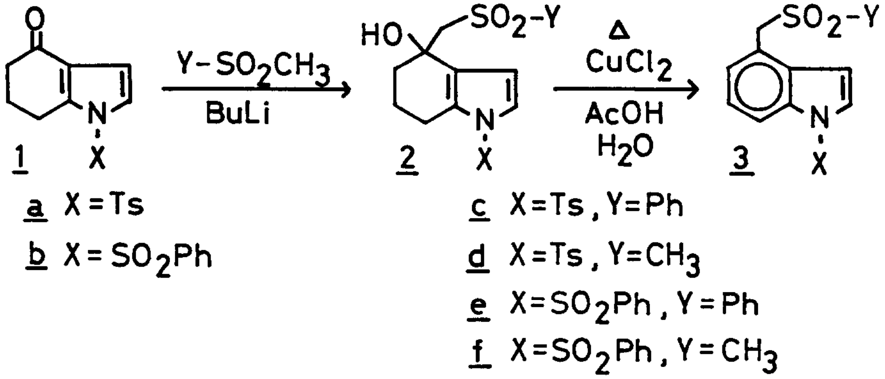
Summary: A facile and short procedure for 4-(sulfonylmethyl)indole synthesis from 4-oxo-4,5,6,7-tetrahydroindole is developed and formal total synthesis of 6,7-secoagroclavine is completed to prove the versatility of this sulfone.

Synthesis of 4-substituted indoles has been extensively explored because this class of compounds including ergot alkaloids have interesting biological activities.[1] Although most of synthetic efforts toward 4-substituted indoles start from 4-formylindole derivatives, methods for its preparation have been quite limited.[2] The best one devised so far is Leimgruber-Batcho approach,[3] which still is not practical enough for large scale operation. We have been working on a totally different approach which utilizes 4-oxo-4,5,6,7-tetrahydroindole derivatives such as 1.[4] Since compound 1 has a convenient handle (carbonyl group), nucleophile's attack on carbonyl and subsequent oxidation should provide a variety of 4-substituted indoles. In order to exploit this strategy further, we have planned to put in sulfonylmethyl group because it enables us to generate anion next to the sulfone and to make carbon extention reactions using electrophiles.[5,6]

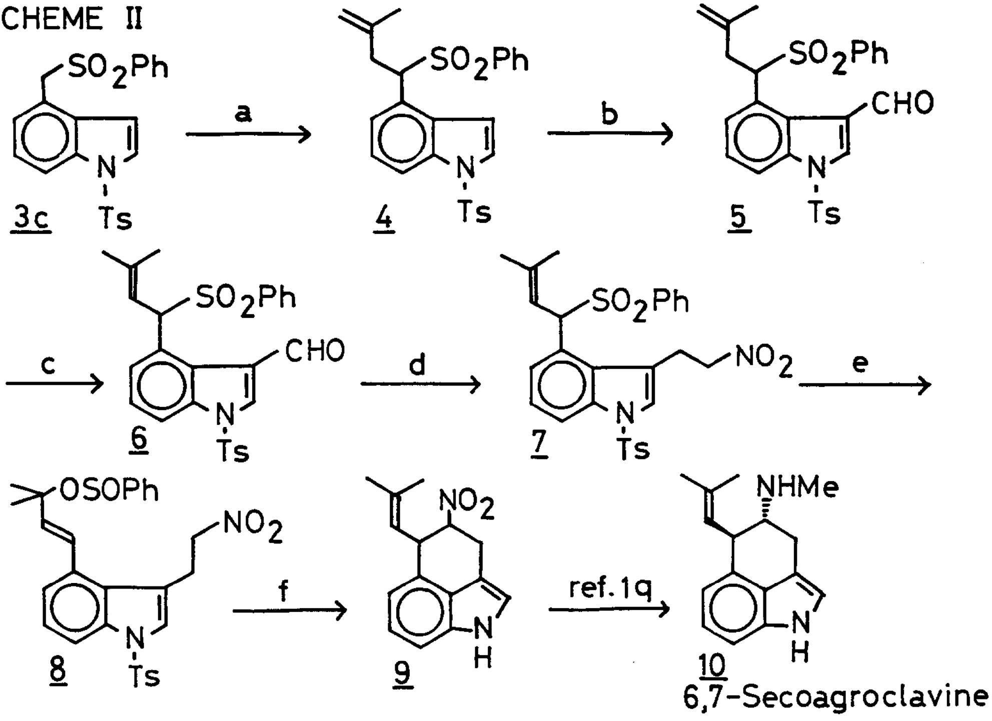
Anion of dimethyl sulfone (Y = CH_3) or methyl phenyl sulfone (Y = Ph) can be generated with butyllithium in tetrahydrofuran at - 78 °C in 2 h. When the reaction was complete, thick slurry of the anion formed. The anion (1.2 eq.) reacted with 4-oxotetrahydroindoles 1 to produce adducts (2c - 2f) in good yields (- 78 °C - 0 °C, 4. h). The adducts with 1a (2c and 2d) could be recrystalized from toluene in excellent yields (1a→2c, 95.8 %; 1a→2d, 87.7 %). The adducts (2e and 2f) remained sticky and amorphous, and so were used for the next reaction without purification. The adducts 2 were dehydrated and dehydrogenatively oxidized with cupric chloride (2.2 eq) in refluxing aqueous acetic acid (5 h) to afford 4-(sulfonylmethyl)indole derivatives in a single step (yields for 2 to 3 transformation: 2c→3c, 86.6 %; 2d→3d, 81.1 %; 1b 2e→3e, 68.9 %; 1b→2f→3f, 66.1 %).

Versatile intermediate sulfone 3 in hand, we set out for an application of this sulfone approach, namely synthesis of an indole alkaloid, 6,7-secoagroclavine 10. Anion of sulfone 3 (BuLi, 1.1 eq., THF, - 78 °C, 1 h) was alkylated with methallyl tosylate (1.2 eq.) to give a side-chain extended

SCHEME I



SCHEME II



a) butyllithium (1.2 eq), THF, - 78 °C, 1 h; methallyl tosylate (1.2 eq.), - 78 °C - 0 °C, 3 h. b) NaOMe (3.3 eq.), MeOH - THF, 50 °C, 18 h; $POCl_3$ - DMF (3eq.), THF, room temperature, 30 min; NaH (2.2 eq.), THF, room temperature, 12 h; TsCl (2.4 eq.), room temperature, 1 h. c) $(PhCN)_2PdCl_2$ (7.5 mol %), $ClCH_2CH_2Cl$, 70 °C, 20 h. d) NH_4OAc (5 eq.), CH_3NO_2 - AcOH 10:1, 90 °C, 1 h; $NaBH_4$ (3 eq., CH_2Cl_2 - MeOH 4:1, 0 °C, 10 min. e) $ZnCl_2$ (1.2 eq.), CH_2Cl_2, room temperature, 12 h. f) KOH (6eq.), MeOH, reflux, 12 h.

product 4 (- 78 °C - 0 °C, 3 h; 92.1 %). In order to introduce formyl group at 3-position, tosyl group was removed first (NaOMe, 3.3 eq., MeOH - THF, 50 °C, 18 h; 86.7 %). After formyl group was introduced using Vilsmeyer reagent ($POCl_3$ - DMF, 3 eq., THF, R.T., 30 min; 96.2 %), tosyl group was put back on nitrogen (NaH, 2.2 eq., THF, R.T., 12 h; TsCl, 2.4 eq., R.T., 1 h; 97.2 %) to produce aldehyde 5. Double bond migration was effected with palladium catalyst[7] [$(PhCN)_2PdCl_2$, 7.5 mol %, $ClCH_2CH_2Cl$, 70 °C, 20 h, 100 %] to form allylic sulfone 6. Condensation of formyl group with nitromethane (NH_4OAc, 5 eq., CH_3NO_2 - AcOH 10:1, 90 °C, 1 h, 58.9 %) and subsequent reduction ($NaBH_4$, 3 eq., CH_2Cl_2 - MeOH 4:1, 0 °C, 10 min, 91.8 %) yielded nitro compound 7.

1,3-Type migration of sulfone was effected under the influence of Lewis acid ($ZnCl_2$, 1.2 eq., CH_2Cl_2, R.T., 12 h; 88.5 %) to provide a cyclization precursor, allylic sulfinate ester 8. Although this type of unusual rearrangement could not be found in the literature as far as the authors could search, intramolecular Friedel-Crafts type alklylation of allylic sulfone under the influence of Lewis acid has been reported.[6f] This fact surely suggests a migratory nature of sulfone and sulfinate ester may be a possible intermediate for this Friedel-Crafts reaction of allylic sulfone as well. Cyclization and simultaneous removal of tosyl group to 9 was achieved with pottasium hydroxide in methanol (KOH, 6 eq, MeOH, reflux, 12 h; 40 %). Thus obtained 9 was 2:1 cis-trans mixture[8] and cis-isomer may be converted to trans-isomer with sodium methoxide in methanol.

Since trans-5-(2-methyl-1-propenyl)-4-nitro-1,3,4,5-tetrahydro[cd]indole 9 has been transformed to d,l-6,7-secoagroclavine 10 by Somei and coworkers,[1q] formal total synthesis of 10 was completed through our new sulfone approach.

As one of our ongoing project of 4-substituted indole synthesis from 4-oxo-4,5,6,7-tetrahydroindole we have prepared 4-(sulfonylmethyl)indole derivatives and completed a formal total synthesis of 6,7-secoagroclavine using this versatile intermediate. Other use of 4-oxotetrahydroindole has been investigated and will be reported shortly.

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8. cis-Isomer 9: NMR ($CDCl_3$) δ 1.66 (d, J=1.3 Hz, 3H), 1.82 (d, J=1.4 Hz, 3H), 3.35 (dd, J=15.8 Hz, J=4.7 Hz, 1H), 3.55 (dd, J=15.8 Hz, J=10.4 Hz, 1H), 4.76 (dd, J=10.4 Hz, J=4.5 Hz, 1H), 4.97 (dt, J=10.8 Hz, J=4.6 Hz, 1H), 5.16 (broad d, J=10.3 Hz, 1H), 6.88(dd, J=6.3 Hz, J=0.9 Hz,1H), 6.93 (s, 1H), 7.13 - 7.21 (m, 2H) and 8.03 (broad s, 1H) ppm.

   trans-Isomer 9: Mp 148 - 150 ° C (purified by sublimation). NMR ($CDCl_3$) δ 1.77 (d,J=1.3 Hz,3H), 1.83 (d, J=1.3 Hz,3H), 3.51 (d, J=6.4 Hz, 2H), 4.55 (t, J=9.8 Hz, 1H), 4.72 -4.84 (m, 1H), 5.14-5.17 (m, 1H), 6.83 (dt, J=6.6 Hz, J=1.3 Hz, 1H), 6.91 (s, 1H), 7.13 - 7.21 (m, 2H) and 8.03 (broad s, 1H) ppm. IR (KBr) 3420, 1540, 1445, 1370, 1350 and 750 cm^{-1}. Mass (m/z, %) 256 (M^+, 53), 209 (80), 208 (47), 194 (100), 167 (36) and 154 (74). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found:C, 69.89; H, 6.46; N, 10.68.

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