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A CONCISE ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF SEMPERVIRINE[1]

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Abstract: Diels-Alder reaction of 5-acetyl-3-methylthio-1,2,4-triazine **3** with 1-pyrrolidino-1-cyclohexene afforded 3-acetyl-1-methylthio-5,6,7,8-tetrahydroisoquinoline **4** which was readily converted into target 2-(3-(5,6,7,8-tetrahydroisoquinolinyl))indole **6** via Fisher synthesis followed by reductive cleavage of the methylthio group in **5.**

Sempervirine **7** is representative of a family zwitterionic indole alkaloids represented by serpentine, alstonine, flavopereirine and indolo[2,3-a]quinolizine, some of which show both strong affinity for DNA and novel antitumor activity[2]. The alkaloid was originally isolated in 1916 from the bark and leaves of Gelsenium sempervirens[3]. Since Woodward's synthesis of N-methylsempervirine[4] in 1949 many research groups paid attention to sempervirine[5]. Until now only one succesful synthesis of sempervirine itself based on pyridine - nitrogen directed beta - lithiation and subsequent annulation of appropriately substituted 2-(3-(5,6,7,8-tetrahydroisoquinolinyl))indole **6** was reported by Gribble[6]. Preparation of **6** a key intermediate in Gribble's synthesis of sempervirine involves a multistep procedure starting from cyclohexanone (eight steps)[7] or from

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[1] *Dedicated to Prof.Nelson J.Leonard in the occasion of his 80th birthday*

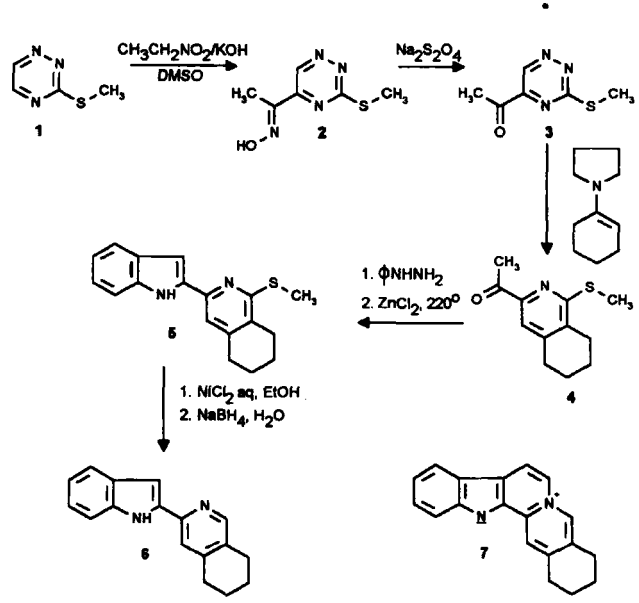
1(phenylsulfonyl)indole (seven steps)[6]. In this communication we develop a new concise route to that intermediate in five chemical steps from easily available 3-methylthio-1,2,4-triazine **1**. This approach evolved from developments in direct nucleophilic acylation of 1,2,4-triazines with nitronate anions[8] and in 1,2,4- triazine annulation chemistry[9]. The essential features of the strategy are summarized in the sequence depicted in the scheme, wherein **3** was envisaged as a key intermediate and the primary subgoal of the project. Inverse electron demand (LUMO diene controlled) Diels-Alder reaction of the latter with enamine should provide the desired teterahydroisoquinoline intermediate **4** which may be converted into target molecule via Fischer indole synthesis, followed by reductive cleavage of the methylthio group in **5.**

The required oxime **2** was obtained via regioselective nucleophilic substitution of 5-hydrogen in 3-methylthio- 1,2,4-triazine **1** with ethanenitronate according to our published method[8]. The cleavage of the protecting group in **2** by using sodium dithionite in aqueous dioxane gave 5-acetyl-3-methylthio-1,2,4-triazine **3** in good isolated yield. The reaction of the latter with 1-pyrrolidino-1-cyclohexene proceeded smoothly under relatively mild conditions within a few hours to afford compound **4** in 81 % yield.

Treatment of the compound **4** with phenylhydrazine in boiling ethanol in the presence of a catalytical amount of acetic acid gave phenylhydrazone which was immediately converted to the 2-(3-(1-methylthio-5,6,7,8-tetrahydroisoquinolinyl))indole **5** by heating in 1-methylnaphtalene with zinc chloride.Attempts to remove the methylthio group in **5** with zinc foil in acetic acid failed. However conversion to **6** was effected by reductive cleavage of the methylthio group with sodium borohydride in the presence of nickel (II) chloride hexahydrate[10].

In conclusion, this synthetic route is quite convenient for preparation of sempervirine using 2-(3-(5,6,7,8-tetrahydroisoquinolinyl))indole as a key intermediate. The method should be of general use for the synthesis of related natural products and analogs.

Scheme



Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. The IR spectra were recorded on a Unicam SP - 200 instrument. The NMR spectra were recorded from deuteriochloroform on Varian Gemini 200 spectrometer. Mass spectra measurements were caried out with AMD-604 Inectra spectrometer.

The starting 3-methylthio-1,2,4-triazine **1** was prepared in one step from glyoxal and (S)-methylthiosemicarbazide according to published method[11].

Methyl 3-(Methylthio)-1,2,4-triazin-5-yl Ketone Oxime 2: To a stirred suspension of powdered potassium hydroxide (10 g) in anhydrous DMSO (50 ml) a solution of **1** (3.81 g, 30 mmol) and nitroethane (4.5 g, 60 mmol) in anhydrous DMSO (5 ml) was

added dropwise at 20-25°C.The mixture was stirred at this temperature for 1h and then was poured into ice/water (300 ml) and acidified with acetic acid to pH 6.4. The precipitated solid was collected by filtration and washed with water to give oxime **2** (3.84 g, 70%) which was used as such in the next step. An analytical sample of **2** could be obtained after one recrystallization from water/ethanol, m.p.151°C. ^{1}H NMR δ: 2.12(s, 3H), 2.61(s, 3H), 9.37(s, 1H), 12.67(bs, 1H).

$C_6H_8N_4OS$(184.2) Calcd. C 39.12 H 4.38 N 30.41

Found C 39.07 H 4.28 N 30.24

Methyl 3-(Methylthio-) 1,2,4-triazin-5-yl Ketone 3: The oxime **2** (2.76 g, 15 mmol) was dissolved in 50% aqueous dioxane (50 ml) containing sodium dithionite (6.09 g, 35mmol). The mixture was stirred 24 h at room temperature. After that time dioxane was evaporated in vacuo and a slight excess of 2 M hydrochloric acid was added to the reaction mixture. Nitrogen was bubbled through the mixture to expel the sulfur dioxide.Solid sodium carbonate was added to alkanity. The aqueous mixture was allowed to stand for 1 h and was extracted with chloroform (5 x 20 ml). The combined extracts were dried and evaporated in vacuo.Purification of the crude product with a silica - gel column using a mixture of chloroform/acetone in the ratio 10:1 as eluent afforded pure **3** (1.61 g, 64%), m.p.39-40°C. IR (KBr) ν:1720 (CO st); ^{1}H NMR δ : 2.70 (s,3H), 2.75 (s,3H), 9.32 (s,1H).

$C_6H_7N_3OS$ (169.2) Calcd. C 42.59 H 4.17 N 24.83

Found C 42.59 H 4.18 N 24.48

3-Acetyl-1-methylthio-5,6,7,8-tetrahydroisoquinoline 4: A solution of the ketone **3** (1.07 g, 6.3 mmol) and 1-pyrrolidino-1-cyclohexene (1.81 g, 12.6 mmol) in dry benzene (30 ml) was refluxed for 4 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure. Purification of the oily residue

with a silica-gel column using a mixture of chloroform - hexane in the ratio 1:1 as eluent afforded pure **4** (1.13 g, 81%), m.p.62-63°C. IR (KBr) ν:1700 (C0 st); ^{1}H NMR δ:1.22-1.42 (m,4H) ,2.61(m,5H) 2.70 (s,3H), 2.76 (t,2H), 7.65 (s,1H).

$C_{12}H_5N0S$ (221.3) Calcd. C 65.12 H 6.83 N 6.33

Found C 64.87 H 6.79 N 6.73

2-(3-(1-Methylthio-5,6,7,8-tetrahydroisoquinolinyl))indole 5: A solution of **4** (0.61 g, 2.75 mmol) and phenylhydrazine (0.29 g, 2.75 mmol) in ethanol (10 ml) containing ten drops of acetic acid was refluxed for 10 min.The solvent was evaporated in vacuo.To the residue was added zinc(II)chloride (3.15 g, 20 mmol) and 1-methylnaphtalene (8 ml). A mixture was heated with stirring at 210-220°C under argon for 2.5 h.1-Methylnaphtalene was decanted from the cold mixture. The resulting solid was well spreaded, treated with water (10 ml), toluene (20 ml) and heated on a water-bath for 1 h. The toluene layer together with toluene extracts of the aqueous layer (10 ml) was evaporated under vacuum.Purification of the residue with a silica-gel column using a mixture of chloroform-hexane in the ratio 1:1 as eluent afforded pure **5** (0.44 g, 55%), m.p.106-107°C. IR (KBr) ν:3450 (NH); ^{1}H NMR δ:1.72-1.96 (m,4H), 2.60 (t ,2H J=6.1 Hz), 2.70 (s, 3H), 2.76 (t, 2H J=6.0 Hz), 6.92 (s,1H), 7.05-7.25 (m, 3H), 7.44-7.63 (m, 2H), 9.32 (s,1H).

$C_{18}H_{18}N_2S$ (294.4) Calcd. C 73.43 H 6.16 N 9.51 S 10.89

Found C 73.41 H 6.05 N 9.04 S 10.81

2(3-(5,6,7,8-Tetrahydroisoquinolinyl)) indole 6: To a solution of **5** (0.029 g,0.1 mmol) in ethanol (2 ml) was added under argon $NiCl_2 \cdot 6\,H_20$ (0.237 g , 1 mmol). The mixture was cooled to 0°C with stirring. To a stirred mixture was added dropwise a solution of $NaBH_4$ (0.11 g, 3 mmol) in water (2 ml) at 0°C. After stirring for 2 h at 0°C under argon the mixture was allowed to warm slowly to room temperature. The

precipitated solid was filtered and washed with ethanol (1 ml). The combined filtrates were rotoevaporated. Purification of the crude product with a silica-gel plates (eluent :chloroform-hexane in the ratio 1:2) afforded pure **6** (0.015 g, 60%), m.p.158-159^{0}C (described[6] 159-160^{0}C).HRMS, m/z 248.13135 (Calcd. for $C_{17}H_{16}N_2$, 248.13133).

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