Reaction of Tris(alkylthio)cyclopropenyl Cations with 2-Pyridylmagnesium Bromide as a New Route to Indolizines

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The reaction of tris(isopropylthio)- and tris(*tert*-butylthio)cyclopropenylium perchlorates **1a** and **1b** with 2-pyridylmagnesium bromide in dry tetrahydrofuran at room temperature gave 1,2,3-tris(isopropylthio)- and 1,2,3-tris(*tert*-butylthio)indolizines **2a** and **2b**, respectively, in high yields.

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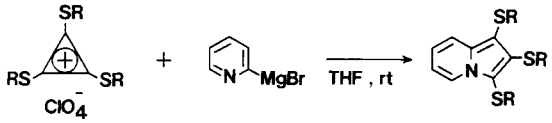
The cyclopropenyl cations are of interest in serving as a three-carbon building block in organic synthesis [1]. Recently, we have reported that tris(isopropylthio)cyclopropenylium perchlorate (**1a**) reacts with pyrrolyl *N*-anions to give pyrrolizines through the formation of a vinylcarbene intermediate by ring opening [2]. In the course of our studies on the synthesis of nitrogen heterocycles using the cyclopropenyl cations, we carried out the reaction of **1a** and tris(*tert*-butylthio)cyclopropenylium perchlorate (**1b**) with the nucleophile bearing the $-\bar{C}=N-$ moiety. We now report our findings that the reaction of **1a** and **1b** with 2-pyridylmagnesium bromide gives 1,2,3-tris(isopropylthio)- and 1,2,3-tris(*tert*-butylthio)indolizines **2a** and **2b**, respectively, in high yields (Scheme 1).

Scheme 1



1

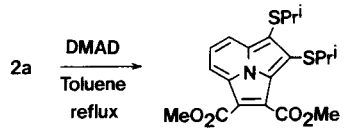
a ; R = Pr^i
b ; R = Bu^t

2

a ; R = Pr^i
b ; R = Bu^t

The reaction was carried out as follows. The cyclopropenyl cation **1a** or **1b** was added under argon to a solution of 2-pyridylmagnesium bromide, prepared from 2-bromopyridine and magnesium metal in the presence of 1,2-dibromoethane [3], in dry tetrahydrofuran (THF) and the mixture was stirred at room temperature for 30 minutes. Extractive workup with dichloromethane and subsequent chromatography gave the indolizines **2a** and **2b** in 99 and 72% yields respectively. The ^{13}C nmr spectra of **2a** and **2b** showed eight signals for the indolizine ring carbons at δ 106.0, 111.6, 116.7, 117.9, 120.3, 124.3, 133.1 and 138.7 and at δ 108.5, 111.6, 119.2, 120.1, 120.5, 125.4, 134.1 and 139.7, respectively, which corresponded to those of indolizine described previously [4]. To obtain further evidence for the formation of the indolizine nucleus, we carried out the reaction of **2a** with dimethyl acetylenedicarboxylate (DMAD) in boiling toluene for 40 hours, since it has been reported previously that indolizine [5] and 3-hydrazinoindolizine [6] are converted into cycl[3.2.2]azine-1,2-dicarboxylate by reaction with DMAD. Consequently, it was demonstrated that dimethyl 3,4-bis(isopropylthio)cycl-[3.2.2]azine-1,2-dicarboxylate (**3**) was obtained as yellow crystals (mp 79-80°) in 96% yield (Scheme 2). The structure of **3** was established by the measurements of the ^1H

Scheme 2

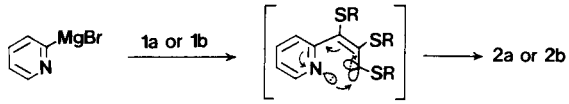


3

nmr and ^{13}C nmr spectra. Its ^1H nmr spectrum showed three signals (3H, δ 7.94, 8.04 and 8.40) for the aromatic protons, two singlets (6H, δ 4.01 and 4.11) for the methyl protons of two methoxy groups and two doublets (12H, δ 1.27 and 1.31) and two septets (2H, δ 3.50 and 3.84) for the methyl and methine protons of two isopropylthio groups, respectively. Its ^{13}C nmr spectrum showed ten signals (10C, δ 111.6, 113.3, 116.8, 122.9, 124.1, 125.4, 125.8, 129.2, 134.3 and 134.7) for the cyclazine ring carbons and two signals (2C, δ 164.0 and 165.8) due to two carbonyl groups. Furthermore, it was confirmed that the reaction of **1a** and **1b** with pyridine, used instead of 2-pyridylmagnesium bromide, does not give **2a** and **2b** respectively.

The reaction of 2-pyridylmagnesium bromide with **1a** and **1b** is explained to proceed through the formation of

Scheme 3



4

a ; R = Pr^i
b ; R = Bu^t

the vinylcarbene intermediates **4a** and **4b** by the nucleophilic attack of 2-pyridylmagnesium bromide on **1a** and **1b**, followed by intramolecular cyclization of vinylcarbenes with the nitrogen atom to give **2a** and **2b** respectively (Scheme 3).

The above results provide a convenient and relatively efficient method for the preparation of indolizines using a cyclopropenyl cation as an annulating reagent.

EXPERIMENTAL

Melting points were determined with a Yanaco MP-S3 melting point apparatus and are uncorrected. All ^{1}H nmr (270 MHz) and ^{13}C nmr (68 MHz) spectra were determined on a JEOL JNM-GX 270 FT nmr spectrometer using deuteriochloroform as a solvent and chemical shifts are reported in parts per million down field from tetramethylsilane as an internal standard. The ir spectra were obtained on a Hitachi 215 spectrophotometer. The uv spectra were obtained on a Shimadzu UV-160 spectrophotometer. Mass spectra were obtained on a Shimadzu LKB-9000 spectrometer (70 eV). Elemental analyses were performed by a Yanaco CHN CORDER MT-3.

Reaction of the Cyclopropenyl Cations **1a** and **1b** with 2-Pyridylmagnesium Bromide.

1,2-Dibromoethane (282 mg, 1.5 mmoles) and 2-bromopyridine (237 mg, 1.5 mmoles) were added under argon to a suspended solution of magnesium metal (73 mg, 3 mmoles) in dry tetrahydrofuran (5 ml) at room temperature. The mixture was stirred until magnesium metal dissolved completely and the cyclopropenyl cation **1a** (181 mg, 0.5 mmole) or **1b** (210 mg, 0.5 mmole) was added to the solution in one portion. The solution was stirred at room temperature for 30 minutes and then a saturated aqueous ammonium chloride solution was added. The mixture was extracted with dichloromethane (2 x 50 ml) and the extract was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the chromatography of the residual oil on silica gel with dichloromethane-hexane (1:3) as the eluent gave the indolizines **2a** (168 mg, 99%) and **2b** (137 mg, 72%).

1,2,3-Tris(isopropylthio)indolizine (**2a**).

This compound was obtained as a yellowish oil, bp 130°/2 mm Hg; ir (neat): ν max 2960, 2920, 2870, 1620, 1490, 1435, 1375, 1345, 1325, 1265, 1225, 1145, 1045, 995, 920, 870, 820, 740, 730 cm^{-1}; ^{1}H nmr: δ 1.18 (d, 6H, J = 6.7 Hz, CH*Me*$_2$), 1.19 (d, 6H, J = 6.7 Hz, CH*Me*$_2$), 1.21 (d, 6H, J = 6.7 Hz, CH*Me*$_2$), 3.26 (sep, 1H, J = 6.7 Hz, C*H*Me$_2$), 3.30 (sep, 1H, J = 6.7 Hz, C*H*Me$_2$), 3.88 (sep, 1H, J = 6.7 Hz, C*H*Me$_2$), 6.66 (m, 1H, 6-H), 6.89 (m, 1H, 7-H), 7.65 (m, 1H, 8-H), 8.49 (m, 1H, 5-H); ^{13}C nmr: δ 23.1, 23.2, 23.3, 38.7, 39.9, 40.4, 106.0, 111.6, 116.7, 117.9, 120.3, 124.3, 133.1, 138.7; uv (acetonitrile): λ max (ϵ) 223 (20900), 266 (20900), 321 (4900) nm; ms: m/z 339 (M$^+$).

Anal. Calcd. for $C_{17}H_{25}NS_3$: C, 60.13; H, 7.42; N, 4.12. Found: C, 60.41; H, 7.68; N, 4.22.

1,2,3-Tris(*tert*-butylthio)indolizine (**2b**).

This compound was obtained as colorless crystals, mp 134-135°; ir (potassium bromide): ν max 2960, 2900, 1500, 1480, 1460, 1370, 1350, 1330, 1230, 1170, 1150, 1070, 1005, 750, 735, 690 cm^{-1}; ^{1}H nmr: δ 1.23 (s, 9H, Bu^t), 1.24 (s, 9H, Bu^t), 1.26 (s, 9H, Bu^t), 6.66 (m, 1H, 6-H), 6.90 (m, 1H, 7-H), 7.73 (m, 1H, 8-H), 8.70 (m, 1H, 5-H); ^{13}C nmr: δ 31.3, 31.5 (2C), 48.6, 49.0 (2C), 108.5, 111.6, 119.2, 120.1, 120.5, 125.4, 134.1, 139.7; uv (acetonitrile): λ max (ϵ) 231 (20900), 253 (20900), 321 (5400) nm; ms: m/z 381 (M$^+$).

Anal. Calcd. for $C_{20}H_{31}NS_3$: C, 62.99; H, 8.14; N, 3.67. Found: C, 62.82; H, 8.34; N, 3.81.

Reaction of the Indolizine **2a** with Dimethyl Acetylenedicarboxylate.

Dimethyl acetylenedicarboxylate (1.42 g, 10 mmoles) was added under argon to a solution of the indolizine **2a** (170 mg, 0.5 mmole) in dry toluene (5 ml) and the mixture was stirred under reflux for 40 hours. The solvent was removed *in vacuo* and the chromatography of the residual oil on silica gel with dichloromethane-hexane (3:1) as the eluent gave the cyclazine **3** (194 mg, 96%) as yellow crystals, mp 79-80°; ir (potassium bromide): ν max 2955, 2945, 2860, 1735, 1710, 1485, 1455, 1445, 1395, 1330, 1300, 1290, 1285, 1235, 1205, 1185, 1165, 1105, 1030, 785 cm^{-1}; ^{1}H nmr: δ 1.27 (d, 6H, J = 6.7 Hz, CH*Me*$_2$), 1.31 (d, 6H, J = 6.7 Hz, CH*Me*$_2$), 3.50 (sep, 1H, J = 6.7 Hz, C*H*Me$_2$), 3.84 (sep, 1H, J = 6.7 Hz, C*H*Me$_2$), 4.01 (s, 3H, OMe), 4.11 (s, 3H, OMe), 7.94 (t, 1H, J = 7.3 Hz, aromatic), 8.04 (d, 1H, J = 7.3 Hz, aromatic), 8.40 (d, 1H, J = 7.3 Hz, aromatic); ^{13}C nmr: δ 23.5 (2C), 40.2, 40.7, 51.8, 52.9, 111.6, 113.3, 116.8, 122.9, 124.1, 125.4, 125.8, 129.2, 134.3, 134.7, 164.0, 165.8; uv (acetonitrile): λ max (ϵ) 259 (31620), 360 (6900), 423 (12600) nm; ms: m/z 405 (M$^+$).

Anal. Calcd. for $C_{20}H_{23}NO_4S_2$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.14; H, 5.73; N, 3.16.

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