

A New Route to Pyridine Derivatives by the Reaction of Tris(isopropylthio)cyclopropenylium Perchlorate with α -Lithiated Isocyanides

Hideo Kojima and Kazuhiko Yamamoto

Laboratory of Organic Chemistry, Osaka Women's University,
Sakai, Osaka 590, Japan

Yasuo Kinoshita and Hiroo Inoue*

Department of Applied Chemistry, College of Engineering,
University of Osaka Prefecture,
Sakai, Osaka 593, Japan

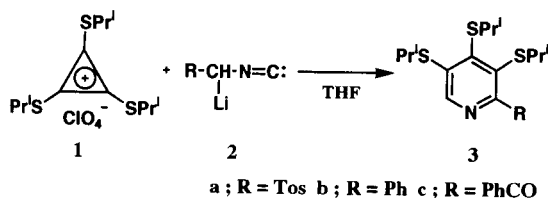
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The reaction of tris(isopropylthio)cyclopropenylium perchlorate (**1**) with α -lithiated tosylmethyl, benzyl and benzoylmethyl isocyanides **2a-c** in dry tetrahydrofuran gave the pyridine derivatives **3a-c** respectively.

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The cyclopropenyl cations are of great value as a three-carbon building block for constructing heterocyclic systems. Recently, we have reported that tris(isopropylthio)cyclopropenylium perchlorate (**1**) reacts with pyrrolysodium, 2-pyridylmagnesium bromide and 2-lithiated azoles to give pyrrolizine [1], indolizine [2,3] and pyrrolo[2,1-*b*]azole derivatives [3], respectively, in high yields. The reactions are explained to proceed through the formation of a vinylcarbene intermediate which undergoes intramolecular cyclization. We now report a novel method for preparing pyridine derivatives **3a-c** via the vinylcarbene intermediates from **1** and α -lithiated isocyanides **2a-c** (Scheme 1).

Scheme 1

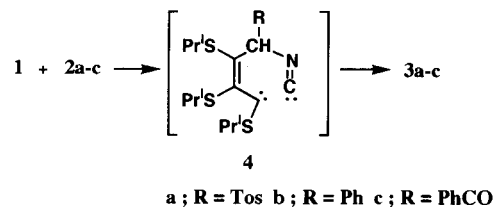


The reaction of **1** with α -lithiated tosylmethyl isocyanide **2a** was carried out as follows. The cyclopropenyl cation **1** was added under nitrogen to a solution of **2a** (1 equivalent), prepared from tosylmethyl isocyanide and butyllithium, in dry tetrahydrofuran (THF) at -60° and the mixture was allowed to warm to room temperature. After 3 hours, an aqueous ammonium chlorides solution was added. Extractive workup with dichloromethane and subsequent chromatography gave 3,4,5-tris(isopropylthio)-2-tosylpyridine (**3a**) in 80% yield. The structure of **3a** was established by the measurements of the ^1H nmr and ^{13}C nmr spectra. Its ^1H nmr spectrum showed a singlet (1H, δ 8.23) for the pyridine ring proton, two doublets (4H, δ 7.32 and 7.92) for the benzene ring protons, a singlet (3H, δ 2.44) for the methyl protons of the tosyl group, and three septets (3H, δ 3.57, 3.79 and 3.89) and three doublets (18H,

δ 1.01, 1.23 and 1.41) for the methyl and methine protons of the isopropylthio groups respectively. Its ^{13}C nmr spectrum showed signals (11C, δ 129.1, 129.6, 136.3, 137.3, 142.7, 144.2, 146.2, 151.0 and 157.6) for the pyridine and benzene ring carbons. The reaction of **1** with α -lithiated benzyl isocyanide **2b** (2 equivalents) in dry THF at room temperature for 15 hours gave 3,4,5-tris(isopropylthio)-2-phenylpyridine (**3b**) in 60% yield. In this reaction, the optimal molar ratio of **2b** to **1** was 2:1. The reaction of **1** with α -lithiated benzoylmethyl isocyanide **2c** (1 equivalent), prepared from 5-phenyloxazole and butyllithium [4], gave 2-benzoyl-3,4,5-tris(isopropylthio)pyridine (**3c**) in 37% yield after 15 hours. The structures of **3b** and **3c** were elucidated by similar methods described above. The lowering of the yields of **3b,c** was due to the formation of unidentified products by a side reaction.

Compounds **3a-c** are considered to be produced by the intramolecular cyclization of the vinylcarbene of the intermediates **4a-c**, prepared from **1** and **2a-c**, to the isonitrile carbene, accompanied by hydrogen migration (Scheme 2).

Scheme 2



The above results provide a novel method for the preparation of pyridine derivatives using the cyclopropenyl cation **1** as a synthetic reagent.

EXPERIMENTAL

Melting points were determined with a Yanaco MP-S3 melting point apparatus and are uncorrected. All ^1H 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 Cyclopropenyl Cation **1** with α -Lithiated Tosylmethyl Isocyanide **2a**.

A solution of butyllithium (1.6 mmoles) in hexane (1 ml) was added under nitrogen to a solution of tosylmethyl isocyanide (293 mg, 1.5 mmoles) in dry tetrahydrofuran (THF) (10 ml) at -60° and the mixture was stirred for 30 minutes. The complete formation of **2a** was ascertained by the ^1H nmr analysis of the deuterium oxidized-treated mixture. The cyclopropenyl cation **1** (541 mg, 1.5 mmoles) was added to the solution at -60° and the mixture was allowed to warm to room temperature. After 3 hours, an aqueous ammonium chloride solution was added and the mixture was extracted with dichloromethane (300 ml). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane-dichloromethane (5:1) as the eluent to give 3,4,5-tris(isopropylthio)-2-tosylpyridine (**3a**) (546 mg, 80%) as yellow oil; ir (neat): ν max 3090, 3070, 3020, 2975, 2925, 2875, 1600, 1455, 1390, 1375, 1325, 1310, 1300, 1150, 1080, 1050, 845, 820, 710, 670 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.01 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.23 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.41 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 2.44 (s, 3H, Me), 3.57 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.79 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.89 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 7.32 (d, 2H, $J = 7.9\text{ Hz}$, aromatic), 7.92 (d, 2H, $J = 7.9\text{ Hz}$, aromatic), 8.23 (s, 1H, pyridine ring); ^{13}C nmr (deuteriochloroform) δ 21.7, 22.6, 22.7, 23.2, 36.2, 40.4, 41.0, 129.1, 129.6, 136.3, 137.3, 142.7, 144.2, 146.2, 151.0, 157.6; uv (acetonitrile): λ max (ϵ) 288 (14800) nm; ms: m/z 455 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_2\text{S}_4$: C, 55.35; H, 6.41; N, 3.07. Found: C, 55.47; H, 6.64; N, 2.98.

Reaction of Cyclopropenyl Cation **1** with α -Lithiated Benzyl Isocyanide **2b**.

A solution of butyllithium (3.2 mmoles) in hexane (2 ml) was added under nitrogen to a solution of benzyl isocyanide (0.38 ml, 3 mmoles) in dry THF (10 ml) at -60° and the mixture was stirred for 30 minutes. After the complete formation of **2b** was ascertained, the cyclopropenyl cation **1** (541 mg, 1.5 mmoles) was added to the solution and the mixture was allowed to warm to room temperature. After 15 hours, the mixture was treated by the method being similar to the case of **2a**. The chromatography of the products on silica gel using hexane-dichloromethane (2:1) as

the eluent gave 3,4,5-tris(isopropylthio)-2-phenylpyridine (**3b**) (339 mg, 60%) as yellow oil; ir (neat): ν max 3050, 2960, 2920, 2870, 1520, 1490, 1450, 1410, 1385, 1370, 1325, 1320, 1250, 1170, 1155, 1050, 750, 695 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 0.96 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.31 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.41 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 2.91 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.58 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.89 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 7.39-7.42 (m, 3H, aromatic), 7.65-7.69 (m, 2H, aromatic), 8.40 (s, 1H, pyridine ring); ^{13}C nmr (deuteriochloroform) δ 22.8, 22.9, 23.2, 36.6, 39.4, 40.5, 127.9, 128.1, 129.4, 135.6, 138.5, 141.0, 146.0, 149.6, 159.1; uv (acetonitrile): λ max (ϵ) 280 (15200) nm; ms: m/z 377 (M^+).

Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{NS}_3$: C, 63.61; H, 7.21; N, 3.71. Found: C, 63.44; H, 7.21; N, 3.94.

Reaction of Cyclopropenyl Cation **1** with α -Lithiated Benzoylmethyl Isocyanide **2c**.

A solution of butyllithium (1.6 mmoles) in hexane (1 ml) was added under nitrogen to a solution of 5-phenyloxazole (218 mg, 1.5 mmoles) in dry THF (10 ml) at -60° and the mixture was stirred for 30 minutes. After the complete formation of **2c** was ascertained, the cyclopropenyl cation **1** (541 mg, 1.5 mmoles) was added to the solution and the mixture was allowed to warm to room temperature. After 15 hours, the mixture was treated by the method being similar to the case of **2a**. The chromatography of the products on silica gel using hexane-dichloromethane (5:1) as the eluent gave 2-benzoyl-3,4,5-tris(isopropylthio)pyridine (**3c**) (225 mg, 37%) as yellow oil; ir (neat): ν max 3075, 2970, 2930, 2875, 1685, 1600, 1455, 1390, 1385, 1325, 1295, 1250, 1215, 1180, 1160, 1060, 970, 710 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.11 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.29 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 1.43 (d, 6H, $J = 6.7\text{ Hz}$, CHMe_2), 3.53 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.63 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 3.97 (sep, 1H, $J = 6.7\text{ Hz}$, CHMe_2), 7.42-7.47 (m, 2H, aromatic), 7.54-7.61 (m, 1H, aromatic), 8.40 (s, 1H, pyridine ring); ^{13}C nmr (deuteriochloroform) δ 22.8, 23.1, 23.2, 36.6, 40.1, 41.0, 128.5, 129.9, 133.5, 133.9, 136.3, 141.7, 145.9, 150.2, 157.8, 193.8; uv (acetonitrile): λ max (δ) 237 (28500) nm; ms: m/z 405 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NOS}_3$: C, 62.18; H, 6.71; N, 3.45. Found: C, 61.99; H, 6.77; N, 3.27.

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