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DIHYDROISOBENZOFURANS AND ISOINDOLINES BY INTRAMOLECULAR INVERSE DIELS-ALDER REACTIONS OF PYRIDINES

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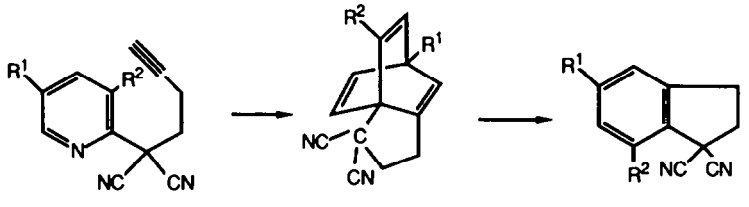
Abstract: Pyridines being substituted at position 2 or 3 with a silylated propynyloxymethyl side-chain undergo a thermolytic intramolecular Diels-Alder reaction with formation of dihydroisobenzofurans. The 3-substituted pyridines are found to be more reactive than the 2-substituted ones. Substitution of both hydrogens in the methylene group at the α-position of this side-chain by one methyl as well as one phenyl substituent leads to a considerable increase of the reaction rate.
In a similar way, from the N-acetyl derivative of 3-trimethylsilyl-propynylaminomethylpyridine, the isoindoline system is formed. The rate of the reaction is considerably lower than that of the corresponding propynyloxymethyl derivative.

In our ongoing research on ring transformations of pyrimidines and pyrazines by a thermolytically induced intramolecular Diels-Alder cycloaddition reaction we extended this study to reactions with appropriately substituted pyridine derivatives. We already found that by thermolysis of the 2-substituted 3(5)-nitropyridine **1** nitroindenes **3** are obtained[1]. This result strongly suggests the intermediacy of the cycloadduct **2**, being obtained by cycloaddition of the triple bond across the C_2-C_5 position of the pyridine ring.



1 **2** **3**

Two questions can be raised: first, is the presence of the electron withdrawing nitro substituent in the pyridine ring, which lowers the LUMO energy level and therefore promotes the cycloaddition, necessary? and secondly is it possible that the cycloaddition over the C_2-C_5 position also takes place when the side-chain is present at C-5 and not, as in **1**, on position 2. Indications

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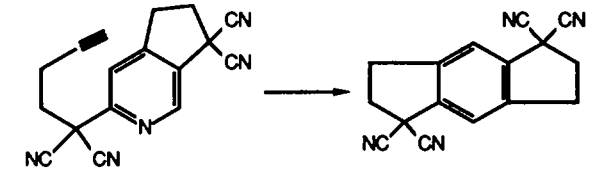
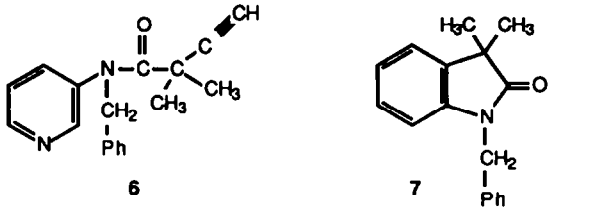
that both questions can positively be answered can be taken from the recently reported[2,3] conversion of the pyridine derivatives **4** and **6** into the s-indacene derivative **5** and indolinone **7** respectively.

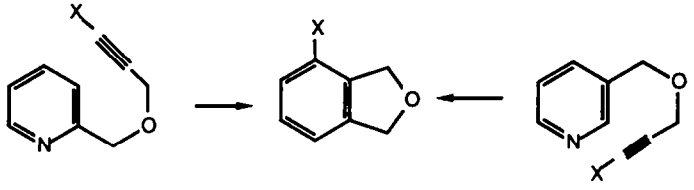


4 **5**



6 **7**

We have found before[4] that heating of pyrazines, which show the presence of a trimethylsilyl group at the terminal carbon atom of the triple bond usually gives cleaner reactions with less decomposition, when undecane instead of nitrobenzene is used as solvent, although the reaction rate in undecane is considerably lower. In this paper we deal with the synthesis and the thermolysis of pyridines, in which on position 2 or on position 3 of the pyridine ring a trimethylsilylpropynyl-X-methyl (X=O,N) side chain is present. Furthermore we compared the reactivities of these respective compounds and studied the influence of the presence of one or more substituents in the side chain on their thermolysis rates.



8 **10** **9**

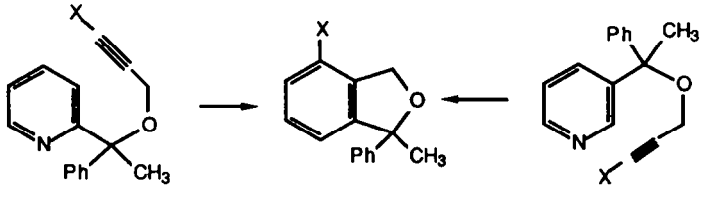
a) X = H; b) X = $Si(CH_3)_3$; c) X = $Si(Ph)_2tBu$

Compounds **8a** and **9a**, being prepared from 2- and 3-pyridylcarbinol respectively by reaction with 3-bromopropyne, gave on heating only polymeric material together with some carbinol. However, the corresponding trimethylsilyl derivatives **8b** and **9b**, being synthesized from **8a** and **9a** by lithiation with phenyllithium and subsequent treatment with trimethylsilyl chloride, gave on heating at 195° in undecane 4-trimethylsilyl-1,3-dihydroisobenzofuran(**10b**). The yield of **10b** obtained from **9b** after 154 hours of heating amounted to 40%; the yield of**10b** after 216 hrs of

heating of **8b** was 27%. These results indicate that the internal cycloaddition over the C_2-C_5 position in **8b** occurs less easily than that over the C_3-C_6 position in **9b**. The attack of the terminal triple bond carbon, being negatively charged due to the electron donating effect of the trimethylsilyl group, on C_5 in **8b** apparently occurs less easily than addition to the more positively charged C_6 position in **9b**.

Replacement of the trimethylsilyl group in **9b** by the more bulky t-butyldiphenylsilyl group i.e. **9c** leads to a considerable increase of reaction time. Only after thermolysis for 440 hrs (!) in undecane the starting material **9c** was disappeared; product **10c** was obtained in only 22% yield. Considerable steric hindrance seems to be the retarding factor in the reaction.

In a previous paper[4] we proved that the presence of a phenyl group in the α–position of an ω–alkyne side chain attached to a pyrazine ring leads to a strong enhancement of the rate of the intramolecular Diels-Alder reaction. In order to establish whether this phenomenon could also be observed in pyridine systems we synthesized the 2- and 3-substituted pyridines **11, 12**. Treatment of 2(3)-pyridylphenylmethylcarbinol[5,6] with 3-bromopropyne in basic medium gave the compounds **11a, 12a**. Silylation and germanylation according to described procedures gave **11b** and **12b,c** respectively.



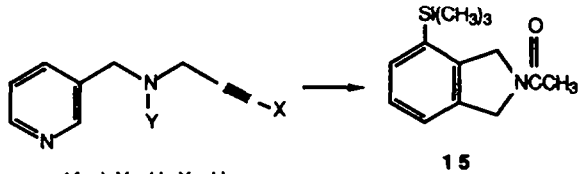
11 **13** **12**

a) X = H, b) X = Si $(CH_3)_3$, c) X = Ge $(CH_3)_3$

From the results given in Table 1 it can be seen that the compounds **11b, 12b** and **12c** can easily be converted into the corresponding dihydroisobenzofurans **13b,c** in reasonable-to-good yields. Moreover it can be concluded that the rate of the intramolecular Diels-Alder reaction in **11b** and **12b,c** is considerably higher than in case of the compounds **8b** and **9b**. This rate increase due to the presence of the methyl and phenyl group in the α–position of the side-chain is considerable as can be deduced from the fact that the difference in rate, as observed between the compound **8b** and **9b**, is nearly equalized between **11b** and **12b**. Similar effects have been observed before[7,8,9] in related systems and can be ascribed to either the Thorpe-Ingold effect[10] and/or a more favoured orientation of the alkynyl side-chain towards the pyridine ring, making overlap between the HOMO and LUMO orbitals more effective.

In extension of this study we also investigated the trimethylsilyl 3-(N-acetyl-N-2-propynyl) aminomethylpyridine **14c**. This compound was prepared from 3-aminomethylpyridine by alkynylation with 3-bromopropyne and subsequent treatment of the secondary amino group

with acetyl chloride. The trimethylsilyl derivative was obtained according to known procedures. Thermolysis of **14c** (see table 1) gave the isoindoline **15** in low yield. The rate of the reaction is lower than that of the corresponding oxygen compound **9b**.



14 a) Y = H, X = H

b) Y = $COCH_3$, X = H

c) Y = $COCH_3$, X = $Si(CH_3)_3$

15

Table 1. Reaction conditions, products and yields in the Diels-Alder cyclisations of silylated (germanylated) propynyloxymethylpyridines and propynylaminomethylpyridine in undecane as a solvent.

Starting material	Reaction time (hrs) at 195°C	Yield of product %
8b	216	**10b** (27)
9b	154	**10b** (40)
9c	440	**10c** (22)
11b	23	**13b** (60)
12b	24	**13b** (74)
12c	31	**13c** (67)
14c	360	**15** (19)

EXPERIMENTAL SECTION

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer. Me_4Si was used as internal standard (δ=0ppm.). Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with VG ZAB console. Column chromatography was carried out over Merck silica gel 60(230-400 mesh ASTM). Undecane was purchased from Aldrich Chemie (Brussels, Belgium).

2-(2-propynyloxymethyl)pyridine (**8a**) and 3-(2-propynyloxymethyl)pyridine (**9a**)

To a solution of 7.0 g (0.064 mol) of 2- or 3-pyridylcarbinol in 150 ml of dry tetrahydrofuran were added 1.6 g (0.07 mol) of sodium. The mixture was stirred for 24 h at room temperature under nitrogen. To the resulting suspension was added a solution of 8.0 g (0.067 mol) of 3-bromopropyne in 20 ml of dry tetrahydrofuran. The mixture was stirred at room temperature for 4 h. 100 Ml of ether and 20 ml of water were added. The pH of the water layer was diminished to 8 with a few drops of dilute hydrochloric acid. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography of the residue on silica gel (using the solvent system ether/petroleum ether 40-60°, 1:2) gave 5.2 g (55%) of **8a** and (using the solvent system ether/petroleum ether 40-60°, 1:1) gave 5.3 g (56%) of **9a**.

Compound **8a**: Ms Calcd. for C_9H_9NO (M^+): m/e 147.0684. Found: m/e 147.0686. Anal. Calcd. for C_9H_9NO: C, 73.5; H, 6.2; N, 9.5. Found: C, 73.7; H, 6.3; N, 9.7. ^1H NMR ($CDCl_3$) δ 8.60 (d, J=4.8 Hz, 1H), 7.82-7.10 (m, 3H), 4.75 (s, 2H), 4.28 (d, J=2.4Hz, 2H), 2.46 (t, J=2.4 Hz, 1H).

Compound **9a:** Ms Calcd. for C_9H_9NO (M^+): m/e 147.0684. Found: m/e 147.0684. Anal. Calcd. for C_9H_9NO: C, 73.5; H, 6.2; N, 9.5. Found: C, 73.2; H, 6.3; N, 9.5.
^1H NMR ($CDCl_3$) δ 8.59 (m, 2 H, α), 7.72 (dt, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H, γ), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H, β), 4.62 (s, 2H), 4.21 (d, J = 2.4 Hz, 2H), 2.60 (t, J = 2.4, 1H).

α-methyl-α-phenyl-α-(2-propynyloxy)-2-methylpyridine (**11a**) and α-methyl-α-phenyl-α-(2-propynyloxy)-3-methylpyridine (**12a**)
To a solution of 2.0 g (0.01 mol) of 2- or 3-pyridylphenylmethylcarbinol[5,6] in 30 ml of dry tetrahydrofuran were added 0.34 g (0.011 mol) of 80% suspension of sodium hydride. The mixture was stirred for 3 h at room temperature under nitrogen. To the resulting suspension was added a solution of 2.6 g (0.022 mol) of 3-bromopropyne in 10 ml of dry tetrahydrofuran. The mixture was stirred at 70°C for 2 h. After cooling 50 ml of ether and 10 ml of water were added and the pH of the water layer was adjusted between 8 to 9 with solid sodium bicarbonate. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The liquid residue after column chromatography on silica gel (solvent system ether/petroleum ether 40-60°, 1:1) gave 0.65 g (27%) of **11a** and (ether as eluent) gave 0.72 g (30%) of **12a.**
Compound **11a:** Ms Calcd. for $C_{16}H_{14}NO$ (M–1): m/e 236.1075. Found: m/e 236.1075.
The accurate mass of m/e 236 has been measured. Peak m/e 237 is a double peak of the ^{13}C satellite peak of the (M-1) peak and the parent peak itself. The masses of these peaks are not separated at the used resolving power.
Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.0; H, 6.4; N, 5.9. Found: C, 81.4; H, 6.7; N, 6.1. ^1H NMR ($CDCl_3$) δ 8.56 (d, J=4.8Hz, 1H), 7.82-7.08 (m, 8H), 4.05 (d, J=2.4Hz, 2H), 2.38 (t, J=2.4Hz, 1H), 2.06 (s, 3H).

Compound **12a:** Ms Calcd. for $C_{16}H_{15}NO$ (M^+): m/e 237.1150. Found: 237.1152. Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.0; H, 6.4; N, 5.9. Found: C, 80.7; H, 6.7; N, 5.6. ^1H NMR ($CDCl_3$) δ 8.67 (d, J=2.4Hz, 1H, α), 8.52 (dd, J_1=4.8Hz, J_2=1.5Hz, 1H, α), 7.73 (dt, J_1=8.4Hz, J_2=1.5Hz, 1H, γ), 7.52-7.12 (m, 6H), 4.0 (d, J=2.4Hz, 2H), 2.40 (t, J=2.4, 1H), 2.0 (s, 3H).

3-(N-2-propynyl)aminomethylpyridine (**14a**)
To a solution of 5.0 g (0.046 mol) of 3-aminomethylpyridine in 50 ml of dry tetrahydrofuran were added 10 ml of triethylamine and 6.0 g (0.05 mol) of 3-bromopropyne. The mixture was stirred for 4h at 50°C under nitrogen. After filtration the solution was evaporated under reduced pressure. Column chromatography of the residual oil (ether as eluent) gave 1.9 g (28%) of **14a**.
Ms Calcd. for $C_9H_{10}N_2$ (M^+): m/e 146.0844. Found: 146.0838. ^1H NMR ($CDCl_3$) δ 8.59 (m, 2H, α), 7.70 (dt, J_1=8.4Hz, J_2=1.5Hz, 1H, γ), 7.28 (dd, J_1=8.4Hz, J_2=4.8Hz, 1H, β), 3.87 (s, 2H), 3.40 (d, J=2.4Hz, 2H), 2.30 (t, J=2.4Hz, 1H), 1.83 (br s, 1H).

3-(N-acetyl-N-2-propynyl)aminomethylpyridine (**14b**)
To a solution of 1.0 g (0.007 mol) of **14a** in 20 ml of dry tetrahydrofuran was added dropwise a solution of 0.6 g (0.008 mol) of acetyl chloride in 10 ml of dry tetrahydrofuran. The suspension was stirred for 15 min. Solid sodium bicarbonate (1 g) and 15 ml of ether and 1 ml of water were added, and the mixture was stirred for 0.5 h. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Column chromatography of the liquid residue (solvent system methanol/ether/methylene chloride, 1:2:2) gave 1.1 g (83%) of **14b**.
Ms Calcd. for $C_{11}H_{12}N_2O$ (M^+): m/e 188.0950. Found: m/e 188.0950. Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 69.9; H, 6.7; N, 15.1. ^1H NMR ($CDCl_3$) δ 8.59 (m, 2H, α), 7.68 (dt, J_1=8.4 Hz, J_2=1.5Hz, 1H, γ), 7.30 (dd, J_1=8.4Hz, J_2=4.8Hz, 1H, β), 4.68 (s, 2H), 4.20 and 3.93 (d, J=2.4Hz, 2H), 2.30-2.12 (m, 4H). The doublets at δ 4.20 and 3.93 gave on heating of the sample to 60°C one broad signal.

Table 2 Yield, mass spectral, ^1H NMR and elemental analyses data of the silylated compounds **8b, 9b, 9c, 11b, 12b, 14c**, and the trimethylgermanium compound **12c**.

Compound Mp °C	Yield %	MS (M+) Calcd. Found	Anal. Calcd./Found	^1H NMR ($CDCl_3$) δ
8b oil	95	218.1001* 218.1001	C, 65.7; 65.8 H, 7.8; 7.7 N, 6.4; 6.4	8.60 (d, J=4.8Hz, 1H), 7.82-7.11 (m, 3H), 4.72 (s, 2H), 4.30 (s, 2H), 0.18 (s, 9H)
9b oil	81	219.1079 219.1080	C, 65.7; 65.4 H, 7.8; 7.9 N, 6.4; 6.6	8.62 (m, 2H, α), 7.73 (dt, J_1=8.4 Hz, J_2=1.5Hz, 1H, γ), 7.31 (dd, J_1=8.4Hz, J_2=4.8Hz, 1H β), 4.61 (s, 2H), 4.20 (s, 2H), 0.18 (s, 9H)
9c 78-79	66	328.1157** 328.1157	C, 77.9; 77.7 H, 7.1; 7.2 N, 3.63, 3.72	8.62 (m, 2H), 7.9-7.2 (m, 12H), 4.70 (s, 2H), 4.38 (s, 2H), 1.10 (s, 9H)
11b oil	86	309.1549 309.1544	C, 73.7; 74.2 H, 7.5; 7.6 N, 4.5; 4.3	8.53 (d, J=4.8Hz, 1H), 7.80-7.10 (m, 8H), 4.04 (s, 2H), 2.02 (s, 3H), 0.15 (s, 9H)
12b oil	96	309.1549 309.1540	C, 73.7; 73.6 H, 7.5; 7.6 N, 4.5; 4.6	8.68 (d, J=2.4Hz, 1H, α'), 8.50 (dd, J_1=6.0 Hz, J_2=1.5Hz, 1H, α) 7.70 (dt, J_1=8.4Hz, J_2=1.5Hz, 1H, γ), 7.52-7.09 (m, 6H), 3.96 (s, 2H), 1.92 (s, 3H), 0.13 (s, 9H)
12c oil		351.1023 351.1021	C, 64.5; 64.5 H, 6.6; 6.6 N, 4.0; 3.9	8.62 (d, J=2.4Hz, 1H, α'), 8.46 (dd, J_1=4.8Hz, J_2=1.5Hz, 1H, α), 7.70 (dt, J_1=8.4Hz, J_2=1.5Hz, 1H, γ), 7.51-7.10 (m, 6H), 3.93 (s, 2H), 1.88 (s, 3H), 0.30 (s, 9H)
14c oil	62	260.1345 260.1346	C, 64.6; 64.6 H, 7.7; 7.8 N, 4.5; 4.3	8.58 (m, 2H, α), 7.68 (dt, J_1=8.4Hz, J_2=1.5Hz, 1H, γ), 7.28 (dd, J_1=8.4Hz, J_2=4.8 Hz, 1H, β), 4.68 (s, 2H), 4.27 and 4.0*** (s, 2H), 2.20 and 2.10*** (s, 3H), 0.12 (s, 9H)

* Due to the relative intensive (M-1) peak (m/e 218) the accurate mass of the molecular ion of m/e 219 could not be measured properly. That is why the accurate mass of m/e 218 has been measured.

** The molecular ion peak is not visible. The accurate mass of m/e 328 (M-57) has been measured.

*** Sample heating up to 60°C gave one signal.

General procedure for the preparation of the trimethylsilyl derivatives **8b, 9b, 11b, 12b,14c**, the tert-butyldiphenylsilyl derivative **9c** and the trimethylgermanium derivative **12c**

To 0.002 mol of compounds **8a, 9a, 11a, 12a, 14b** dissolved in 10 ml of dry tetrahydrofuran and cooled below -70°C, under nitrogen, a commercial ether-cyclohexane solution of phenyllithium (0.003 mol) was added dropwise while keeping temperature below -65°C. After 5 min 0.003 mol of trimethylsilyl chloride or tert-butyldiphenylsilyl chloride or trimethylgermanium chloride dissolved in 5 ml of dry tetrahydrofuran were added dropwise, keeping temperature below -65°C. After the addition the temperature of the mixture was allowed to rise to -40°C. The mixture was stirred at this temperature for 0.5 h and the temperature was allowed to rise gradually to 0°C during next hour. Then 50 ml of ether and 2 ml of 10% aqueous hydrochloric acid were added. The pH of the water layer was adjusted between 8 to 9 with solid sodium bicarbonate. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The liquid residue after column chromatography on silica gel using the solvent system ether-petroleum ether (40-60°) ratio 1:1 gave **8b, 9b, 11b, 12b, 12c;** for **9c** the ratio 1:2 was used; for **14c** ether/methanol, ratio 20:1 was used. Yield, mass spectral, ^{1}H NMR and elemental analyses data are given in Table 2.

General procedure for the intramolecular Diels-Alder reaction of pyridines **8b, 9b, 9c, 11b, 12b, 12c, 14c**

A solution of 0.3 g of pyridines **8b, 9b, 9c, 11b, 12b, 12c, 14c** in 1 ml of undecane was heated under nitrogen at 195°C (see Table 1 for reaction times). The resultant solution was chromatographed over silica gel; elution with the appropriate solvent system (see Table 3) gave respectively compounds **10b, 10c, 13b, 13c, 15.** Mass spectral, ^{1}H NMR and elemental analyses data are summarized in Table 3.

Table 3 Mass spectral, ^{1}H NMR and elemental analyses data of Diels-Alder products

Products	Mp °C	Ms (M$^+$) Calcd. Found	Anal. Calcd/Found	^{1}H NMR ($CDCl_3$)δ	Column chromatogr. ratio ether / petr. ether 40-60°
10b		192.0972 192.0970	C, 68.7; 68.5 H, 8.4; 8.3	7.53-7.18 (m, 3H), 5.25-5.07 (m, 4H), 0.3 (s, 9H)	1:3
10c	110-113	301.1049* 301.1056	C, 80.4; 80.1 H, 7.3; 7.3	7.98-7.23 (m, 13H), 5.02 (s, 2H), 4.21 (s, 2H), 1.24 (s, 9H)	1:5
13b		267.1205** 267.1203	C, 76.6; 76.6 H, 7.9; 8.2	7.64-7.20 (m, 8H), 5.20 (s, 2H), 1.87 (s, 3H),0.28 (s, 9H)	1:9
13c		309.0673** 309.0680	C, 66.1; 66.3 H, 6.8; 7.1	7.60-7.12 (m, 8H), 5.17 (s, 2H), 1.85 (s, 3H), 0.4 (s, 9H).	1:9
15	93-95	233.1236 233.1235	C, 66.9; 66.8 H, 8.2; 8.5 N, 6.0; 6.0	7.58-7.20 (m, 3H), 4.92-4.68 (2 br s, 4H), 2.15 (s, 3H), 0.31 (s, 9H)	ether as eluent

* The molecular ion peak is not visible. Accurate mass of m/e 301 (M-57) has been measured.

** The molecular ion peak is not visible. Accurate mass has been measured of the peak m/e M-15.

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