HETEROCYCLES, Vol. 66, 2005, pp. 563 – 566. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2005, Accepted, 7th October, 2005, Published online, 11th October, 2005. COM-06-S(K)19

INTERMOLECULAR PHOTOREACTION OF BENZENECARBOTHIOAMIDE WITH γ,δ -UNSATURATED KETONES: APPLICATION TO SYNTHESIS OF CYCLOALKANE [*c*]-FUSED PYRIDINES

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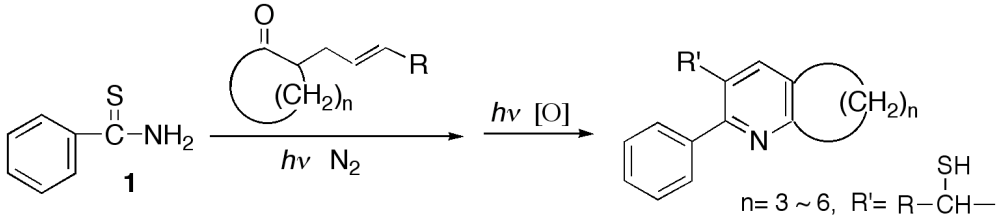
Abstract ––– Irradiation of benzenecarbothioamide with (2-methylenecycloalkyl)acetaldehyde in benzene gives cycloalkane [*c*]-fused pyridines in moderate yields.

Much interest has been shown in pyridine ring-containing compounds due to their widespread occurrence in nature as well as the remarkable versatility of pyridine derivatives in synthetic organic chemistry.[1] In pharmaceutical chemistry, considerable interest has been shown in highly substituted and ring-fused pyridines as antiarterioscleotics since they efficiently inhibit HMG-CoA reductase and cholesterol transport proteins.[2] Although there have been extensive efforts directed to the synthesis of pyridine derivatives, relatively little is known about the synthesis of various-sized cycloalkane-fused pyridines.[3]

We previously reported that arenecarbothioamides undergo a Paterno-Büchi-type reaction with diene-conjugated carbonyl compounds upon irradiation to give 2-arylpyridines.[4] Further, irradiation of benzenecarbothioamide (**1**) with 2-(2-alkenyl)cycloalkanone (an analogue of γ,δ-unsaturated carbonyl compounds) gave cycloalkane [*b*]-fused pyridines (Scheme 1).[5] As an



1

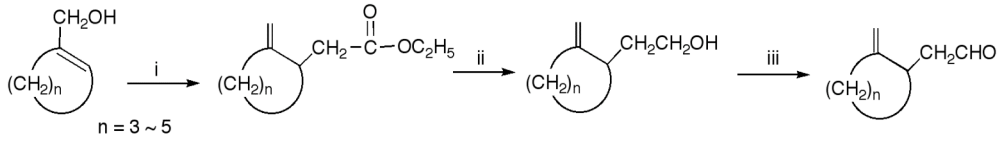
Scheme 1

extension of this reaction, we report here facile synthesis of various-sized cycloalkane [*c*]-fused pyridines through photoreactions of **1** with (2-methylenecycloalkyl)acetaldehydes (**2**).

This paper is dedicated to the memory of the Emeritus Professor K. Koga of Tokyo University.

The synthetic route to a series of (2-methylenecycloalkyl)acetaldehydes (**2**) is outlined in Scheme 2 .

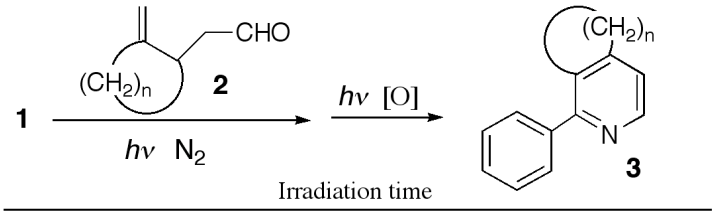
Scheme 2



Reagents: i) $CH_3CH(OC_2H_5)_3$, CH_3CH_2COOH ii) $LiAlH_4$, iii) PCC / CH_2Cl_2

Photoreactions of **1** with **2** were carried with irradiation by a 1 kW high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere for 20-30 h. Further irradiation was carried out for 10 min under an aerobic condition (in the presence of oxygen) to complete an efficient oxidation process. As expected, cycloalkane [*c*]-fused pyridine derivatives (**3**) were obtained in moderate yields (Table 1).

Table 1. Photoreactions of **1** with **2**

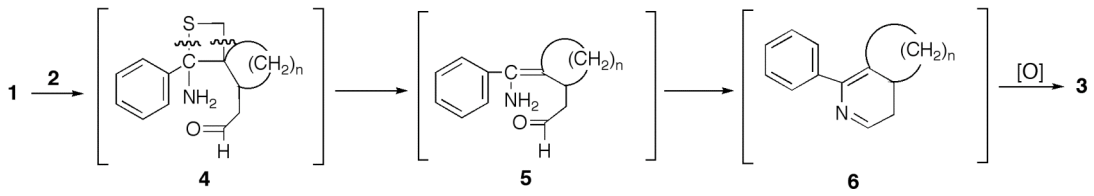


2a: n = 3	30 h	**3a**: 56 %
2b: n = 4	30 h	**3b**: 53 %
2c: n = 5	20 h	**3c**: 62 %

Structures of cycloalkane [*c*]-fused pyridine derivatives (**3**) were assigned on the basis of spectral data and HRMS spectra. For example, the MS spectrum of **3b** showed a molecular ion peak at M^+ 209, suggesting the intermolecular addition of **1** to **2b**. The ^{1}H-NMR spectrum of **3b** showed two doublets (7.00 ppm and 8.34 ppm) with a coupling constant of 5.0 Hz, indicating the presence of 2,3,4-trisubstituted pyridine. In addition, two triplets (two 2H protons at 2.66 ppm and 2.82 ppm with 6.2 Hz as a coupling constant) and a multiplet (4H protons at 1.7-1.8 ppm) indicated the presence of 1,2-disubstituted cyclohexane. Results of ^{1}H-^{1}H COSY, ^{13}C-NMR, DEPT, and ^{1}H-^{13}C COSY spectral experiments confirmed the structure of **3b**.

The results of these experiments suggest that the reaction proceeds in several steps involving initial thietane (**4**) formation between thiocarbonyl and the γ,δ-double bond of the alkenyl moiety in **2**, resulting in the formation of the key ω-aminocarbonyl intermediate (**5**), which subsequently cyclizes to the dihydropyridine derivative (**6**). Ultimately, **6** is aromatized by oxidation as shown

Scheme 3



in Scheme 3.

In conclution, the photoreaction of benzenecarbothioamide with (2-methylenecycloalkyl)-acetaldehydes provides a practical route to the synthesis of cycloalkane [*c*]-fused pyridines. Much attention has been paid to the construction of a pyridine ring in view of the biological activity.[1] Therefore, this photoreaction also may be added as new entry in the synthesis of highly substituted and ring-fused pyridines

ACKNOWLEDGEMENTS

This study was partially supported by the Academic Science Frontier Project of the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We are grateful to the staff of the Center for Instrumental Analysis, Hokkaido University, for the HRMS spectra measurements.

EXPERIMENTAL

All melting points were determined using a Yamato melting point apparatus (model MP-21) and are uncorrected. The IR spectra were recorded using a JASCO A-102 spectrophotometer. The NMR spectra were obtained using JEOL JNM LA300. The chemical shifts are reported in ppm (δ) relative to TMS (0.0 ppm) as the internal standard. The MS spectra (MS, HRMS) were obtained using a Shimadzu GC MS 9100-MK gas chromatograph-mass spectrometer. Preparative irradiations were conducted by using a 1 kW high-pressure mercury lamp (Eikosha EHB-W-1000) through a Pyrex filter at room temperature. Stirring of the reaction mixture was effected by the introduction of a stream of nitrogen at the bottom of the outer jacket. Column chromatography was conducted using silica gel (Merck, Kieselgel 60, 70-230 mesh).

Cycloalkenylmethanols used in this study were prepared according to the references cited: cyclopentenylmethanol,[6] cyclohexenylmethanol,[6] and cycloheptenylmethanol.[7]

Ethyl (2-methylenecyclohexyl)acetate

A mixture containing cyclohexenylmethanol (11.2 g, 0.1 mol), triethyl orthoacetate (113 g, 0.7 mol), and propanoic acid (0.44 g, 6 mmol) was heated at 140 °C for 10 h with slow distillative removal of the ethanol produced. After the mixture had been cooled to rt, propanoic acid and excess triethyl orthoacetate were removed by distillation under reduced pressure [50-60 °C (15 mmHg)]. The title compound (14.2 g, 77%) was then distilled: bp 108-110 °C/ 16 mmHg (lit.,[6] bp 116-119 °C/13 mmHg).

Ethyl (2-methylenecyclopentyl)acetate

72% yield, bp 96-100 °C/ 14 mmHg (lit.,[6] bp 96-98 °C/15 mmHg).

Ethyl (2-methylenecycloheptyl)acetate

60% yield, bp 105-108 °C/ 14 mmHg

2-(2-Methylenecyclohexyl)ethanol

To a suspension of $LiAlH_4$ (4.9 g, 0.13 mol) in dry ether (150 mL) was added dropwise ester (15.6 g , 0.085 mol) at a rate to maintain a gentle reflux. After completion of the addition, the mixture was boiled under reflux with stirring for 3 h. After the mixture had been cooled, the reaction was quenched by dropwise addition of water (5 mL), 15% NaOH (5 mL), and water (10 mL). The resulting white suspension was filtered. The organic solution was dried, concentrated in vacuo, and the residue was distilled under reduced pressure to provide alcohol. 7.8 g (65% yield); bp 102-105 °C/ 16 mmHg (lit.[6] 108-110 °C/13 mmHg).

2-(2-Methylenecyclopentyl)ethanol

58% yield, bp 90-94 °C/ 14 mmHg (lit.,[6] bp 98-101 °C/15 mmHg).

2-(2-Methylenecycloheptyl)ethanol

64% yield, bp 102-105 °C/ 14 mmHg

(2-Methylenecyclohexyl)acetaldehyde (2a):
To a suspension of PCC (23 g, 0.11 mol) in dry ether (700 mL) was added dropwise alcohol (7.8 g, 0.06 mol) in dry ether (26 mL) at rt. After completion of the addition, the mixture was stirred for 3 h. The resulting suspension was filtered. The organic solution was dried, concentrated in vacuo, and the residue was distilled under reduced pressure to provide aldehyde. 5.2 g (70%); bp 60-63 °C/ 16 mmHg (lit.,[8] 61-68 °C/15 mmHg).
(2-Methylenecyclopentyl)acetaldehyde (2b):
63% yield, bp 62-65 °C/ 14 mmHg (lit,[9] bp 96-98 °C/15 mmHg).
(2-Methylenecycloheptyl)acetaldehyde (2c):
60% yield, bp 75-78 °C/ 14 mmHg (lit,[9] bp 42 °C/0.1 mmHg).

Irradiation of Thioamides (1). General Procedure:
A solution of **1** (0.69 g. 5 mmol) and **2a** (1.86 g, 15 mmol) in benzene (200 mL) was irradiated for 30 h under a nitrogen atmosphere. Further irradiation was carried out for 10 min under an aerobic condition. After removal of the solvent *in vacuo*, the residue was chromatographed over a silica gel column (hexane – ethyl acetate, 5 : 1; v/v).

6,7-Dihydro-1-phenyl-5*H*-cyclopenta[*c*]pyridine (3a):
Colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.05 (2H, m,), 2.95 (2H, t, *J*=7.5 Hz), 3.08 (2H, t, *J*=7.5 Hz), 7.13 (1H, d, *J*=5.3 Hz), 7.4-7.8 (5H, m), 8.46 (1H, d, *J*=5.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.0 (t), 32.3 (t), 32.7 (t), 118.5 (d), 127.9 (d). 127.9 (dx2), 128.1 (dx2), 131.7 (s), 139.8 (s), 147.1 (d), 154.0 (s), 154.7 (s); MS *m/z* 195 (M^+). The spectral data of this product were identical to those reported in ref. 10.
5,6,7,8-Tetrahydro-1-phenylisoquinoline (3b):
Colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.7-1.8 (4H, m,), 2.66 (2H, t, *J*=6.2 Hz), 2.82 (2H, t, *J*=6.2 Hz), 7.00 (1H, d, *J*=5.0 Hz), 7.3-7.5 (5H, m), 8.34 (1H, d, *J*=5.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.1 (t), 23.0 (t), 27.5 (t), 29.2 (t), 123.0 (d), 127.7 (d). 128.0 (dx2), 128.8 (dx2), 130.8 (s), 140.6 (s), 145.7 (d), 154.0 (s), 154.7 (s); MS *m/z* 209 (M^+); HRMS Calcd for $C_{15}H_{15}N$: 209.1204. Found: 209.1193.
5,6,7,8-Tetrahydro-1-phenyl-5*H*-cyclohepta[*c*]pyridine (3c):
Colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.4-1.8 (6H, m,), 2.60 (2H, t, *J*=6.2 Hz), 2.85 (2H, t, *J*=6.2 Hz), 7.00 (1H, d, *J*=5.0 Hz), 7.3-7.5 (5H, m), 8.34 (1H, d, *J*=5.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.2 (t), 23.5 (t), 27.7 (t), 29.2 (t), 31.6 (t), 123.2 (d), 126.5 (d). 128.5 (dx2), 129.2 (dx2), 131.1 (s), 140.6 (s), 146.0 (d), 154.1 (s), 153.2 (s); MS *m/z* 223 (M^+); HRMS Calcd for $C_{16}H_{17}N$: 223.1361. Found: 223.1358.

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