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INTERMOLECULAR PHOTOADDITION REACTION OF BENZENECARBOTHIOAMIDE WITH γ,δ-UNSATURATED KETONES: A NOVEL FORMATION OF CYCLOALKANE-FUSED PYRIDINE DERIVATIVES BY PHOTOINDUCED REACTION[1]

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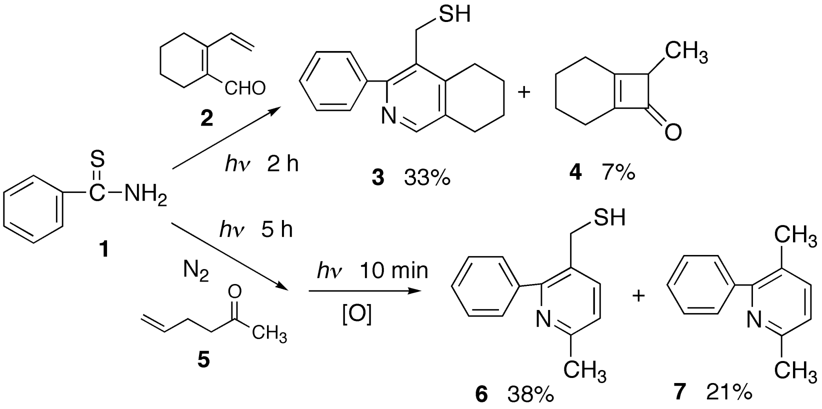
Abstract – Irradiation of benzenecarbothioamide with 2-(2-alkenyl)-cycloalkanone in benzene gives cycloalkane-fused pyridine derivatives in moderate yields.

Fused pyridines[2] such as quinoline and isoquinoline are present in numerous natural products. Because of their structural diversity and interesting bioactivity profile, much interest has been focused on the synthesis of a pyridine ring.[3] Although there has been considerable efforts directed to the synthesis of pyridine alkaloids, relatively little is known about the synthesis of various-sized cycloalkane-fused pyridines.

We previously reported that arenecarbothioamides undergo a Paterno-Büchi-type reaction with diene-conjugated carbonyl compounds upon irradiation to give 2-arylpyridines and 2,6-diarylpyridines.[4] Further, irradiation of benzenecarbothioamide (**1**) with *o*-vinylbenzaldehyde (an analogue of diene-conjugated carbonyl compounds) gave isoquinoline derivatives.[4] As an extension of this reaction, we report here facile synthesis of various-sized cycloalkane-fused pyridine derivatives through photoreaction of **1** with 2-(2-alkenyl)cycloalkanone.

Photoreaction of **1** with 2-vinylcyclohex-1-enecarbaldehyde[5] (**2**) (a diene-conjugated carbonyl compound) in benzene was carried with irradiation by a 1-KW high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere.[6] A tetrahydroisoquinoline derivative (**3**)[7] was obtained in 33% yield together with a small amount of a cyclobutenone derivative (**4**[8] : 7%) (Scheme 1).

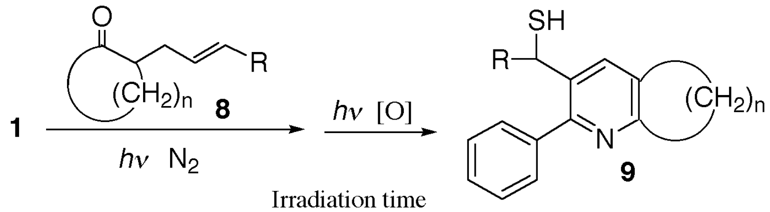
Next, to determine whether the α,β-double bond moiety in diene-conjugated carbonyl compounds is essential for the pyridine ring formation, simple γ,δ-unsaturated ketone (**5**) was selected. Upon irradiation of **1** with hex-5-en-2-one (**5**), two pyridine derivatives (**6**, **7**) were obtained in 21% and 14% yields, respectively (Scheme 1). 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, the yields of **6** and **7** increased to 38% and 21%, respectively. These results suggest that readily available *γ,δ*-unsaturated ketones can serve as equivalents to diene-conjugated carbonyl compounds in photoinduced pyridine ring formation.



Scheme 1

Photoreactions of **1** with a series of 2-(2-alkenyl)cycloalkanones[9] (**8a-e**: γ,δ-unsaturated ketone analogues) were performed under similar conditions. As expected, cycloalkane-fused pyridine derivatives (**9**)[10] were obtained in moderate yields (Table 1).

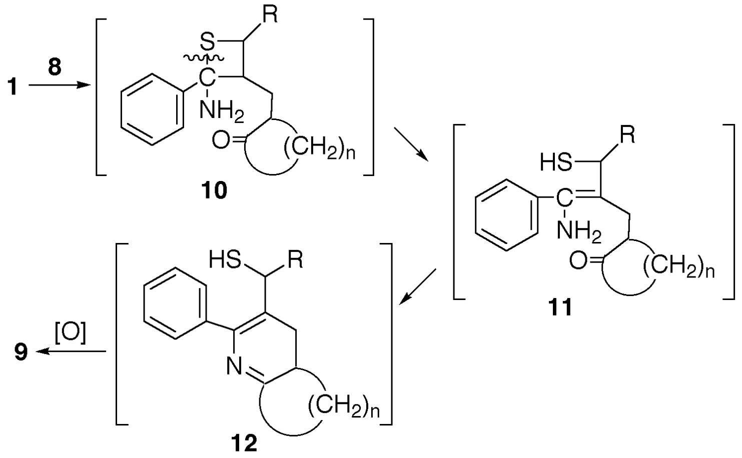
Table 1. Photoreaction of **1** with **8**



	Irradiation time	
8a: n = 3 R = H	20 h	**9a**: 56 %
8b: n = 4 R = H	30 h	**9b**: 53 %[11]
8c: n = 4 R = CH_3	30 h	**9c**: 62 %
8d: n = 5 R = CH_3	20 h	**9d**: 59 %
8e: n = 6 R = CH_3	20 h	**9e**: 55 %

Structures of cycloalkane-fused pyridine derivatives (**9**) were assigned on the basis of spectral data and HRMS specteum. For example, the MS spectrum of **9b** showed a molecular ion peak at M^+ 255, suggesting the intermolecular addition of **1** to **8b**. The ^{1}H-NMR spectrum of **9b** showed a triplet (1.71 ppm) and a doublet (3.67 ppm) with a coupling constant of 7.3 Hz, indicating the presence of thiol proton adjacent to a methylene. In addition, two triplets (two 2H protons at 2.81 ppm and 2.95 ppm with 6.2 Hz as a coupling constant) and a multiplet (4H protons at 1.8-2.0 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 **9b**.

The results of these experiments suggest that reaction proceeds in several steps involving initial thietane (**10**) formation between thiocarbonyl and the *γ,δ*-double bond of the alkenyl moiety in **8**, resulting in the formation of the key *ω*-aminocarbonyl intermediate (**11**), which subsequently cyclizes to the dihydropyridine derivative (**12**). Ultimately, **12** is aromatized by oxidation as shown in Scheme 2.



Scheme 2

In conclusion, photoreaction of benzenecarbothioamide provides a practical route to the synthesis of cycloalkane-fused pyridines. The results of this study also showed that certain readily available γ,δ-unsaturated ketones and their analogues are potentially useful substrates in the photosynthesis of nitrogen-containing heterocycles.

ACKNOWLEDGEMENTS

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6 Irradiation of Thioamides (**1**). General Procedure:

A solution of **1** (1.37 g, 10 mmol) with **2** (4.08 g, 30 mmol) in benzene (200 mL) was irradiated for 2 h under a nitrogen atmosphere. After removal of the solvent *in vacuo*, the residue was chromatographed over a silica gel column (hexane – ethyl acetate, 5 : 1; v/v).

7 (3-Phenyl-5,6,7,8-tetrahydroisoquinolin-4-yl)methanethiol (**3**): mp 114-116 °C (ethanol); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 1H), 1.8-2.0 (m, 4H), 2.81 (t, 2H, *J*=6.2 Hz), 2.90 (t, 2H, *J*=6.2 Hz), 3.66 (s, 2H), 7.4-7.5 (m, 5H), 8.28 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.1 (t), 22.6 (t), 22.7 (t), 25.7 (t), 26.8(t), 127.9 (d), 128.3 (dx2), 128.7 (dx2), 131.7 (s), 132.2 (s), 140.6 (s), 145.0 (s), 146.8 (s), 159.9 (d); MS *m/z* 255 (M^+); HRMS Calcd for $C_{16}H_{17}NS$: 255.1082. Found: 255.1063.

8 This cyclobutenone formation was previously reported in the photocyclization of *o*-vinylbenzaldehyde. S. V. Kessar, A. K. S. Mankotia, J. C. Scaiano, M. Barra, J. Gebicki, and K. Huben, *J. Am. Chem. Soc.*, 1996, **118**, 4361.

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10 (2-Phenyl-5,6,7,8-tetrahydroquinolin-3-yl)methanethiol (**9b**): Colorless oil; ^{1}H-NMR (400 Hz, $CDCl_3$) δ 1.71 (t, 1H, *J*=7.3 Hz), 1.8-2.0 (m, 4H), 2.81 (t, 2H, *J*=6.2 Hz), 2.95 (t, 2H, *J*=6.2 Hz), 3.67 (d, 2H, *J*=7.3 Hz), 7.3-7.5 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.7 (t), 23.2 (t), 25.8 (t), 28.4 (t), 32.4 (t), 128.0 (d), 128.4 (dx2), 128.8 (dx2), 131.2 (s), 131.4 (s), 138.1 (d), 140.0 (s), 155.2 (s), 156.0 (s); MS *m/z* 255 (M^+); HRMS Calcd for $C_{16}H_{17}NS$: 255.1082. Found: 255.1104.

11 3-Methyl-2-phenyl-5,6,7,8-tetrahydroquinoline (**13**) was obtained as a by-product in 8% yield. Presumably, this photoproduct was derived from a thiol derivative (**9b**).[12] In fact, thiol (**9b**) was easily converted to **13** in 68% yield by further irradiation for 5 h.

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