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Efficient syntheses of a novel 5-thia-1-azacycl[3.3.2]azine ring system and 3*H*-1,4-diazacycl[3.3.2]azine derivatives

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Abstract

Novel 5-thia-1-azacycl[3.3.2]azine derivatives **1**, 5-thia-1,8b-diazaacenaphthylenes, have successfully been prepared. An X-ray crystallographic analysis of **1c** revealed that the 5-thia-1-azacycl[3.3.2]azine ring system adopts a planar structure as to the internal ring nitrogen atom. The ¹H NMR spectrum for unsubstituted ring system **1d** implies contribution of a paramagnetic ring current in the peripheral 12π-electron ring system. Also, 3*H*-1,4-diazacycl[3.3.2]azine derivatives, 4-benzyl-4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen(e)-3-ones **2** and -3,5-diones **3** were synthesized with high efficiency via 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine derivatives as new useful synthetic intermediates. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: 5-thia-1-azacycl[3.3.2]azine; 3*H*-1,4-diazacycl[3.3.2]azine; 5-thia-1,8b-diazaacenaphthylene; 4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen-3-one; 4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylene-3,5-dione; 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine.

Cyclazines,¹ fused tricyclic conjugate ring systems linked with three covalent bonds to an internal nitrogen atom, have attracted considerable attention because of interest in their aromatic and antiaromatic properties.² Among cyclazine derivatives, tricyclic fused imidazo[1,2-*a*]pyridines bridged between the C(3) and C(5) positions would be of particular interest because an imidazo[1,2-*a*]pyridine ring system³ has popularly been utilized as a pharmacore for therapeutic drugs⁴ and as a biochemical fluorescent marker⁵ due to its strong fluorescence.⁶ Therefore, it should be intriguing to design and synthesize cyclazine derivatives containing an imidazo[1,2-*a*]pyridine ring system and evaluate their biological activities and fluorescent properties as well as their aromatic or antiaromatic properties.

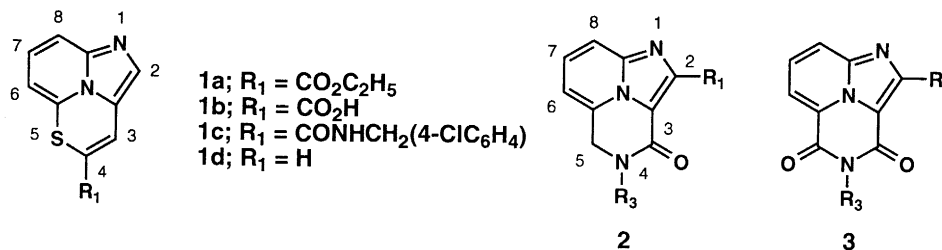
The 5-thia-1,8b-diazaacenaphthylene and 3*H*-1,4,8b-triazaacenaphthylene ring system^{1,7} which could be referred to as 5-thia-1-azacycl[3.3.2]azine and 3*H*-1,4-diazacycl[3.3.2]azine^{1,7} are novel and rarely

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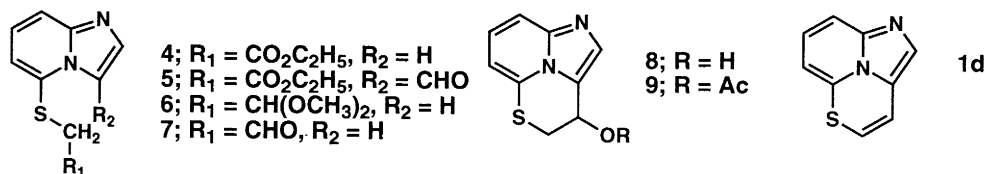
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reported cyclazine derivatives containing an imidazo[1,2-*a*]pyridine ring system. In the present paper, we wish to describe the synthesis and characterization of 5-thia-1,8b-diazaacenaphthylene derivatives **1** (Scheme 1) and syntheses of 4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen(e)-3-ones **2** (Scheme 1) and -3,5-diones **3** (Scheme 1) using 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine derivatives as new synthetic intermediates.



Scheme 1.

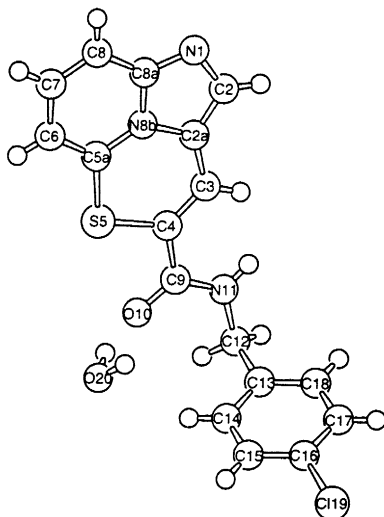
Treatment of ethyl (imidazo[1,2-*a*]pyridin-5-ylthio)acetate **4**⁸ (Scheme 2) with hexamethylenetetramine in acetic acid⁹ or with phosphorous oxychloride in DMF¹⁰ has been found to give 5-thia-1,8b-diazaacenaphthylene-4-carboxylic acid ethyl ester **1a** (Scheme 1) as a purple solid in 95 or 50% yield¹¹ without isolation of 3-carboxaldehyde derivative **5** (Scheme 2). The ester **1a** was subjected to hydrolysis with an aqueous sodium hydroxide solution, and the obtained carboxylic acid **1b** (Scheme 1) was converted into an amide derivative **1c** (Scheme 1). An X-ray crystallographic analysis¹² of **1c** revealed that the structure of the 5-thia-1,8b-diazaacenaphthylene ring system adopts a planar structure as to the internal ring nitrogen atom of the cyclazine molecule (Fig. 1). The bond lengths for C(4)–S(5) and S(5)–C(5a) have been found to be 1.755(3) and 1.775(2) Å which lie between the lengths of a single and a double carbon–sulfur bond,¹³ suggesting that the ring sulfur atom would participate in the π -electron conjugation system.



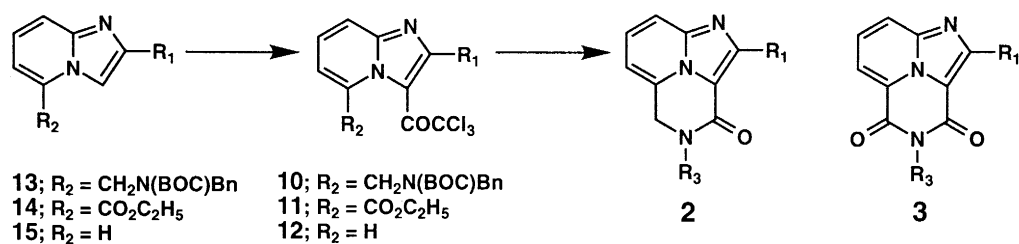
Scheme 2.

Synthesis of the unsubstituted ring system **1d** (Scheme 2) has also been successfully achieved. Hydrolysis of acetal **6** (Scheme 2)¹⁴ and the following intramolecular hydroxyalkylation¹⁵ of **7** (Scheme 2) in acetic acid gave tricyclic fused imidazo[1,2-*a*]pyridine derivative **8** (Scheme 2) in 40% without isolation of **7**. Dehydration of **8** was carried out via acetate **9** (Scheme 2)¹⁶ to afford **1d**¹⁷ in 25% as orange crystals. The chemical shift range for the proton of **1d**¹⁷ has been found to be 5.03–6.75 ppm which is between those of stable ‘aromatic’ (>6.0 ppm)^{2c,f,g,h} and unstable ‘antiaromatic’^{2e,i} (2.1–6.0 ppm) cyclazine ring systems and is similar to those of cycl[3.3.2]azine ring systems containing a sulfur atom (4.95–7.08 ppm).¹⁸ The shielding effect observed would suggest contribution of a paramagnetic ring current in the peripheral 12 π -electron ring system.

3-(Trichloroacetyl)imidazo[1,2-*a*]pyridine **10** and **11** (Scheme 3) are considered to be useful synthetic intermediates for the preparation of (4-alkyl)-4,5-dihydro-3*H*-1,4,8b-triazaacenaphthylen(e)-3-ones **2** (Scheme 3) and -3,5-diones **3** (Scheme 3) as well as various imidazo[1,2-*a*]pyridine-3-carboxylic acid derivatives. It has been well studied that an imidazo[1,2-*a*]pyridine ring system undergoes electrophilic substitution at the C(3) position;¹⁹ however, synthesis of 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine has

Fig. 1. Structure of compound **1c**

not been reported. We have found that treatment of imidazo[1,2-*a*]pyridine **15a** and its derivative **15b**, **15c**, **13**, and **14** bearing substituent(s) at the C(2) and/or C(5) position with excess trichloroacetyl chloride in the presence of excess DMAP²⁰ in refluxing THF for 12 h affords 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine **10–12** in 40–93% (Table 1). Removal of the BOC group of **10** followed by intramolecular displacement of the trichloromethyl group with the resulting amine led to an almost quantitative formation of the corresponding 4-benzyl-4,5-dihydro-3*H*-1,4,8*b*-triazacacenaphthylen-3-ones **2** (Table 1). Also, haloform cleavage of the trichloroacetyl group of **11** with benzylamine in acetonitrile at room temperature in the presence of triethylamine and the following intramolecular condensation gave the corresponding 4-benzyl-4,5-dihydro-3*H*-1,4,8*b*-triazacacenaphthylene-3,5-diones **3** almost quantitatively (Table 1). Furthermore, 3-(trichloroacetyl)imidazo[1,2-*a*]pyridines **12** have been found to be readily converted into the corresponding ester, amide, and free acid by treatment with appropriate alkoxides, ammonia or aliphatic amines, and an aqueous base.



Scheme 3.

In conclusion, we have synthesized 5-thia-1,8*b*-diazacacenaphthylene derivatives and prepared 4,5-dihydro-3*H*-1,4,8*b*-triazacacenaphthylen(e)-3-ones and -3,5-diones with high efficiency via 3-(trichloroacetyl)imidazo[1,2-*a*]pyridine derivatives. The biological activities as well as fluorescent properties of these unique cyclazine derivatives will be reported in the near future.

Table 1
Trichloroacetylation of imidazo[1,2-*a*]pyridine derivatives **13–15**^a and formation of 4,5-dihydro-3*H*-1,4,8*b*-triazacenaphthylene(e)-3-ones **2** and -3,5-diones **3**^b

Imidazo[1,2- <i>a</i>]pyridine			eq. of	Trichloromethyl	4,5-Dihydro-3 <i>H</i> -1,4,8 <i>b</i> - Triazaacenaphthylene ^b		
R ₁	R ₂		CCl ₃ COCl	Ketone ^a		R ₃	(%)
15a	H	H	1	12a	40	–	
15a	H	H	3	12a	93	–	
15b	CH ₃	H	3	12b	60	–	
15c	C ₆ H ₅	H	3	12c	72	–	
13a	H	CH ₂ N(BOC)Bn	3	10a	70	2a	Bn 99
13b	CH ₃	CH ₂ N(BOC)Bn	3	10b	65	2b	Bn 99
14a	H	CO ₂ C ₂ H ₅	3	11a	55	3a	Bn 99
14b	CH ₃	CO ₂ C ₂ H ₅	3	11b	40	3b	Bn 99

a) All the reactions were carried out using 10 mmol of the starting materials **13–15** in the presence of 36 mmol of DMAP.

b) All the reactions were carried out using 10 mmol of the starting materials **10** and **11**.

Acknowledgements

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8. Compound **4** was prepared by treatment of 5-mercaptoimidazo[1,2-*a*]pyridine with ethyl bromoacetate in the presence of triethylamine in ethanol at room temperature in 95% yield.
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11. About 45% of **4** (as **4**·HCl) was recovered. The resulting **4**·HCl in the reaction would not undergo formylation at C(3) with the Vilsmeier's reagent due to low electron density at the C(3) position.
12. Crystal data for **1c**: Formula, C₁₇H₁₂N₃OSCl·H₂O; formula weight, 359.83; crystal system, triclinic; lattice parameters, *a*=8.1693(4) Å, *b*=15.025(1) Å, *c*=7.1614(4) Å, α =103.328(5)°, β =105.603(4)°, γ =88.315(5)°, *V*=823.74(9); space group, P-1 (#2); *Z* value=2; *D*_{calc}=1.451 g/cm³; *R*=0.041 Å³; *R*_w=0.106. Final crystallographic coordinates, bond distances, bond angles, structure factors, and thermal parameters have been deposited with, and can be ordered from, the Cambridge Crystallographic Data Centre.
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16. Compound **9** was prepared by treatment of **8** with acetic anhydride in the presence of DMAP in acetonitrile in 95%.
17. Compound **1d** was prepared by treatment of **9** with DBU in refluxing acetonitrile: mp 112–113°C. IR (KBr) 1613, 1481, 1292 cm^{−1}. ¹H NMR (200 MHz, CDCl₃) δ 5.03 (1H, d, *J*=10.2 Hz), 5.55 (1H, dd, *J*=6.2, 1.0 Hz), 5.85 (1H, d, *J*=10.2 Hz), 6.42–6.58 (2H, m), 6.75 (1H, s). Anal. calcd for C₉H₆N₂S: C, 62.05; H, 3.47; N, 16.08. Found: C, 62.05; H, 3.47; N, 16.09.
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