

Synthesis of Cyclic Imines Having Conjugated Exocyclic Double Bond

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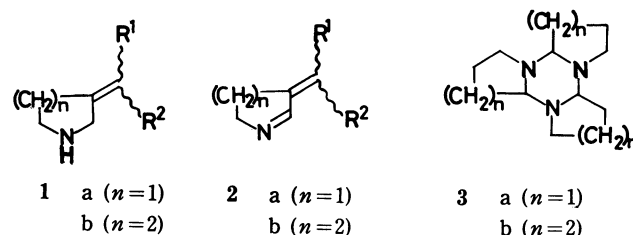
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Synopsis. Cyclic imines with conjugated exocyclic double bond have been synthesized by the reaction of 1-pyrroline trimer or 2,3,4,5-tetrahydropyridine trimer with various aldehydes in methanol in moderate to decent yields.

Cyclic amines possessing the general structure **1** and their quaternary ammonium salts have attracted attention because of their intriguing pharmacological activities. In particular, the five-membered analogs **1a**, in which both R¹ and R² are phenyl, have been known to exhibit potent antihistamine and anticholine activities and indeed some of them have been subjected to clinical applications.¹⁾

The synthesis of these compounds (**1**) heavily depends on the availability of the unsaturated imines (**2**) for which a number of synthetic methods have been reported to date.²⁾ Herein we wish to describe a novel method for the synthesis of **2**.

The new method rests on ready availability of 1-pyrroline trimer (**3a**), the synthesis of which we reported some time ago,³⁾ and 2,3,4,5-tetrahydropyridine trimer (**3b**).⁴⁾ We have now found that these imines react with a variety of aldehydes to give **2** in the yields shown in Table 1.

TABLE 1. REACTION OF **3** WITH ALDEHYDES IN METHANOL

Entry	3	Aldehyde (RCHO) R=	Temp	Time h	Method ^{a)}	Yield %	Mp θ _m /°C
1	a	Ph	r.t.	64	A	28	71.0–71.5 ^{b)}
2	b	Ph	reflux	3	A	40	36.0–38.0 ^{c)}
3	b	Ph	reflux	3	B	38	—
4	b	Ph	r.t.	43	A	39	—
5	b	Ph	r.t.	91	B	50	—
6	b	<i>p</i> -MeC ₆ H ₄	r.t.	111	B	42	47.0–48.0 ^{c)}
7	b	<i>p</i> -MeOC ₆ H ₄	r.t.	108	B	27	73.0–73.5 ^{b)}
8	b	<i>p</i> -Me ₂ NC ₆ H ₄	r.t.	114	B	10	108.5–109.5 ^{d)}
9	b	<i>p</i> -ClC ₆ H ₄	r.t.	87	B	55	oil
10	b	<i>p</i> -NCC ₆ H ₄	r.t.	86	B	56	66.5–67.0 ^{d)}
11	b	<i>p</i> -O ₂ NC ₆ H ₄	r.t.	86	B	74	66.5–67.0 ^{d)}
12	b	<i>i</i> -Pr	r.t.	74	A	37	oil
13	b	2-furyl	r.t.	87	A	77	oil

a) Method A: In the absence of molecular sieves. Method B: In the presence of molecular sieves. b) Recrystallized from hexane. c) Purified by sublimation. d) Recrystallized from cyclohexane.

TABLE 2. SPECTROSCOPIC AND ANALYTICAL DATA FOR **2**

Compd (R ² =H)	R ¹	M ⁺ (<i>m/e</i>)	Found (Calcd) (%)			ν(C=N)/cm ⁻¹	δ _C (C=N) ^{a)}	δ _H ^{a)}
			C	H	N			
2a	Ph	157	83.90 (84.04)	6.92 (7.05)	8.85 (8.91)	1630	168.21	2.77 (m, 2H), 4.13 (m, 2H), 6.73 (t, <i>J</i> =2.5 Hz, 1H), 7.37 (m, 5H), 7.80 (t, <i>J</i> =2.5 Hz, 1H)
2b	Ph	171	84.04 (84.21)	7.73 (7.60)	8.29 (8.19)	1613	163.64	1.71 (qui, <i>J</i> =7 Hz, 2H), 2.70 (dt, <i>J</i> =7, 2.7 Hz, 2H), 3.72 (dt, <i>J</i> =7, 2.7 Hz, 2H), 6.64 (t, <i>J</i> =2.7 Hz, 1H), 7.36 (m, 5H), 7.96 (t, <i>J</i> =2.7 Hz, 1H)
2b	<i>p</i> -MeC ₆ H ₄	185	84.16 (84.28)	7.89 (8.16)	7.83 (7.56)	1597	163.66	1.67 (qui, <i>J</i> =6 Hz, 2H), 2.35 (s, 3H), 2.68 (d, t, <i>J</i> =6, 2.5 Hz, 2H), 3.65 (d, t, <i>J</i> =6, 2.5 Hz, 2H), 6.53 (br s, 1H), 7.16 (m, 4H), 7.93 (t, <i>J</i> =2.5 Hz, 1H)
2b	<i>p</i> -MeOC ₆ H ₄	201	77.64 (77.58)	7.42 (7.51)	6.87 (6.96)	1595	163.64	1.70 (qui, <i>J</i> =6 Hz, 2H), 2.63 (dt, <i>J</i> =6, 2.5 Hz, 2H), 3.63 (dt, <i>J</i> =6, 2.5 Hz, 2H), 3.80 (s, 3H), 6.46 (br s, 1H), 6.83 (d, <i>J</i> =9 Hz, 2H), 7.28 (d, <i>J</i> =9 Hz, 2H), 7.90 (br t, <i>J</i> =2.5 Hz, 1H)
2b	<i>p</i> -NMe ₂ -C ₆ H ₄	214	—	—	—	1592	164.31	1.70 (qui, <i>J</i> =6 Hz, 2H), 2.70 (dt, <i>J</i> =6, 2.5 Hz, 2H), 3.00 (s, 6H), 3.63 (dt, <i>J</i> =6, 2.5 Hz, 2H), 6.47 (br s, 1H), 6.67 (d, <i>J</i> =9 Hz, 2H), 7.28 (d, <i>J</i> =9 Hz, 2H), 7.90 (br s, 1H)
2b	<i>p</i> -ClC ₆ H ₄	205	69.84 (70.07)	6.03 (5.88)	6.64 (6.81) Cl (17.24)	1610	163.28	1.70 (qui, <i>J</i> =6 Hz, 2H), 2.65 (dt, <i>J</i> =6, 2.5 Hz, 2H), 3.67 (br t, 2H), 6.57 (br t, 1H), 7.30 (m, 4H), 7.97 (br s, 1H)
2b	<i>p</i> -CNC ₆ H ₄	196	79.50 (79.56)	6.04 (6.16)	14.23 (14.27)	1605	162.74	1.72 (qui, <i>J</i> =6 Hz, 2H), 2.70 (dt, <i>J</i> =6, 2.7 Hz, 2H), 3.72 (dt, <i>J</i> =6, 2.7 Hz, 2H), 6.62 (br t, <i>J</i> =2.7 Hz, 1H), 7.45 (d, <i>J</i> =9 Hz, 2H), 7.67 (d, <i>J</i> =9 Hz, 2H), 8.01 (t, <i>J</i> =2.7 Hz, 1H)
2b	<i>p</i> -NO ₂ -C ₆ H ₄	216	66.52 (66.65)	5.65 (5.59)	13.22 (12.95)	1605	162.57	1.75 (qui, <i>J</i> =6 Hz, 2H), 2.72 (dt, <i>J</i> =6, 2.7 Hz, 2H), 3.73 (dt, <i>J</i> =6, 2.7 Hz, 2H), 6.67 (br s, 1H), 7.50 (d, <i>J</i> =9 Hz, 2H), 8.02 (t, <i>J</i> =2.7 Hz, 1H), 8.20 (d, <i>J</i> =9 Hz, 2H)
2b	<i>i</i> -Pr	—	—	—	—	1640	163.50	1.00 (d, <i>J</i> =6 Hz, 6H), 1.67 (qui, <i>J</i> =6 Hz, 2H), 2.36 (dt, <i>J</i> =6, 2.5 Hz, 2H), 2.60 (m, 1H), 3.53 (dt, <i>J</i> =6, 2.5 Hz, 2H), 5.53 (br d, <i>J</i> =9 Hz, 1H), 7.77 (t, <i>J</i> =2.5 Hz, 1H)
2b	2-Furyl	167	74.23 (74.51)	6.95 (6.88)	8.49 (8.69)	1605	162.74	1.70 (qui, <i>J</i> =6 Hz, 2H), 2.73 (dt, <i>J</i> =6, 2.5 Hz, 2H), 3.73 (dt, <i>J</i> =6, 2.5 Hz, 2H), 6.37 (t, <i>J</i> =2.5 Hz, 1H), 6.47 (m, 2H), 7.40 (br s, 1H), 7.90 (t, <i>J</i> =2.5 Hz, 1H)

a) In CDCl₃ relative to TMS.

The yields of the reactions involving benzaldehyde (entries 2—5) were about 40% at reflux or room temperature, but the presence of molecular sieves did improve the yield of room temperature reaction (entry 5). It is clear that among para-substituted benzaldehydes (entries 6—11), the yield was significantly increased with electron-withdrawing substituents. As seen in entry 12, the reaction is equally effective for aliphatic aldehydes. The best yield was obtained with 2-furaldehyde (entry 13).

The structures of these conjugated imines (**2**) were elucidated by spectral data (MS, IR, ^1H - and ^{13}C -NMR) as well as by combustion analysis. The presence of conjugated imine moiety was inferred from the following spectral evidence; a strong to medium IR band between 1592 and 1640 cm^{-1} , a low-field doublet near δ 165 in ^{13}C NMR⁵⁾ and a characteristic triplet ($\delta \approx 8$, $J = 2.5$ — 2.7 Hz) in ^1H NMR spectra. A small coupling between allylic methylene protons ($\delta \approx 2.7$, m, 2H) and the exocyclic olefin proton ($\delta \approx 6.5$, t, $^4J = 2.5$ — 2.7 Hz) suggested the trans-relationship of these protons.⁶⁾ The spectroscopic data together with analytical results are summarized in Table 2.

Experimental

Methanol was purified by distillation over sodium under dry nitrogen atmosphere. All reactions were performed under dry nitrogen. Spectral data were obtained by the following spectrometers; Hitachi-Perkin Elmer RMU-6D

mass spectrometer, JASCO DS-403G IR spectrometer, JEOL FX-90Q spectrometer, JEOL MH-100 spectrometer. All chemical shifts are reported in δ relative to internal TMS in CDCl_3 .

General Procedure for the Preparation of 2. A mixture of **3a** or **3b** (2 mmol) and an aldehyde (6 mmol) in methanol (20 ml) was stirred magnetically in the presence or absence of 3A molecular sieves under the conditions indicated in Table 1. After having been stirred for appropriate period (see Table 1), it was concentrated *in vacuo* and the residue purified by silica gel column chromatography. The product was further purified by distillation, sublimation or recrystallization if necessary.

References

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