Synthesis of Cyclic Guanidines Fused with Aromatic Ring through Metal Ion Promoted Cyclization

Hiroyuki OBASE,* Nobuhiro NAKAMIZO, Haruki TAKAI, and Masayuki TERANISHI
Tokyo Research Laboratory, Kyowa Hakko Co., Ltd., Asahimachi 3-6-6, Machida, Tokyo 194

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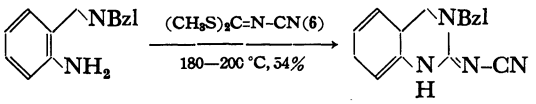
Synopsis. A convenient synthetic method of five- and six- membered cyclic guanidines fused with aromatic ring was presented. 2-Aminoaniline or 2-(aminomethyl)aniline was treated with dimethyl carbonimidodithioates to give isothiourea which was cyclized to cyclic guanidine by using soft metal cations (Ag^+, Hg^{2+}).

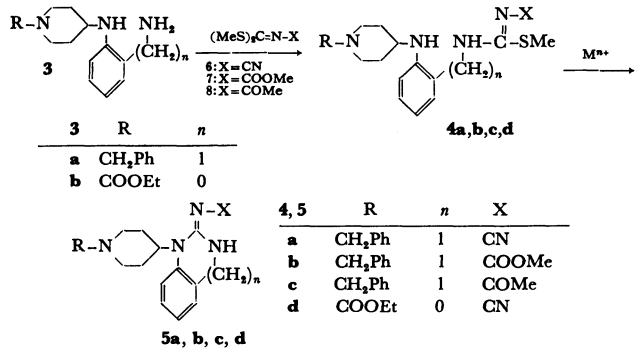
As part of a program directed towards the preparation of potential antiphypertensive agents, it was necessary to synthesize cyclic guanidines fused with aromatic ring under mild conditions. We describe herein a new and mild synthesis of cyclic guanidines with formula **5** which is the key intermediate for the preparation of hypotensive agents, utilizing metal ion promoted reaction.

There are methods available for the synthesis of cyclic guanidines from 2-amino- or 2-(aminomethyl)aniline derivatives.[1-3] However, their syntheses need drastic conditions because of the poor reactivity of an anilino nitrogen. 2-(Cyanoimino)tetrahydroquinazoline **2** has been prepared in 54% yield by heating 2-(benzylaminomethyl)aniline (**1**) with dimethyl cyanocarbonimidodithioate (**6**) at 180—200 °C.[1] Rodricks *et al.* reported



1 **2**

that 2-(tosylamino)benzimidazole could be obtained from the reaction of dimethyl tosylcarbonimidodithioate with *o*-phenylenediamine in DMF at 150—160 °C for 12—16 h.[2] The reactivity of anilino nitrogen in **3** is reduced considerably due to the hindered nature of these molecules. Therefore, the reaction conditions to obtain cyclic guanidine **5** would be more drastic than that reported earlier. Our two-step method is depicted below.



3	R	n
a	CH_2Ph	1
b	COOEt	0

4, 5	R	n	X
a	CH_2Ph	1	CN
b	CH_2Ph	1	COOMe
c	CH_2Ph	1	COMe
d	COOEt	0	CN

The synthesis of cyclization precursor **4** was attained as follows. Wittenbrook and coworker reported the preparation of 2-(cyanoimino)-1*H*-benzimidazole *via* base catalyzed reaction of *o*-phenylenediamine with **6**.[3] However, when 1-ethoxycarbonyl-4-(2-aminoanilino)-piperidine (**3b**) was reacted with **6** under the reaction conditions described by them (using triethylamine as a base, in refluxing ethanol), neither **4d** or **5d** could be detected and unchanged starting materials were recovered. The reaction carried out in dioxane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 80 °C gave an isothiourea **4d** in a moderate yield. In this case, side product such as 2-(methylthio)benzimidazole derivative reported by D' Amico[4] was not detected. The other cyclization precursors **4a**—**c** required for the synthesis of 1,2,3,4-tetrahydroquinazoline **5a**—**c** were obtained in high yields under milder conditions (at room temperature, in ethanol). The yield and physical properties of **4** are summarized in Table 1.

The cyclization of **4** to cyclic guanidine **5** was achieved by using soft metal cations. The result are shown in Table 2.

The kinds of soft metal ion available in this reaction were Hg^{2+} [$HgCl_2$, $Hg(OAc)_2$] and Ag^+ (CH_3COOAg, CF_3COOAg, CH_3SO_3Ag, and CF_3SO_3Ag). The table clearly indicates that the reaction becomes faster as increase with the softness of the metal cations. Cu(I) and Cu(II) did not promote this reaction because of preferential δ or π complexation of amino group to copper.[5-6]

Table 1. Yield and physical properties of compound **4** and **5**

Compd	Yield[a] %	Mp θ_m/°C	IR $\tilde{\nu}$/cm^{-1}		NMR ($CDCl_3$, δ)
4a	92	165—165.5	KBr	2300, 1560—1550	2.51 (s, 3H, SCH_3), 3.55 (s, 2H, CH_2Ph), 4.50 (s, 2H, $ArCH_2NHC$-N)
4b	85	Oil	$CHCl_3$	1640, 1565(br), 1555(br)	2.47 (s, 3H, SCH_3), 3.49 (s, 2H, CH_2Ph), 3.67 (s, 3H, $COOCH_3$), 4.37 (s, 2H, $ArCH_2NHC$-N)
4c	75	Oil	$CHCl_3$	1620, 1583, 1573(sh)	2.11 (s, 3H, $COCH_3$), 2.48 (s, SCH_3), 3.52 (s, 2H, CH_2Ph), 4.29, 4.34 (s, 2H, $ArCH_2NHC$-N)
4d	45	160—161	KBr	2350, 1690—1685 1570	1.27 (t, 3H, CH_3CH_2), 2.35 (s, 3H, SCH_3), 4.17 (q, 2H, CH_2CH_3)
5a	b)	204—205	KBr	2300, 1600, 1585	3.58 (s, 2H, CH_2Ph), 4.28, 4.30 (s, 2H, quinazoline ring H)
5b	b)	120—121	KBr	1633, 1610, 1595, 1582	3.58 (s, 2H, CH_2Ph), 3.73 (s, 3H, $COOCH_3$), 4.27, 4.29 (s, 2H, quinazoline ring H)
5c	b)	104—104.5	KBr	1600, 1575, 1570	2.16 (s, 3H, $COCH_3$), 3.59 (s, 2H, CH_2Ph), 4.26 (s, 2H, quinazoline ring H)
5d	b)	235—235.5	KBr	2330, 1695—1680, 1629, 1609	1.31 (t, 3H, CH_3CH_2), 4.20 (q, 2H, CH_2CH_3), 12.25 (NH)

a) Isolated yield. b) See Table 2.

Table 2. Cyclization of **4** to **5** by metal cations

Starting material	M^{n+}	Conditions[a] Temp/°C	Time/h	Product	Yield[b] %
4a	CF_3COOAg	50	1	**5a**	95
4a	CH_3SO_3Ag	50	2	**5a**	88
4a	CH_3COOAg	50	5	**5a**	90
4a	$Hg(OAc)_2$	20	0.2	**5a**	96
4a	$HgCl_2$	20	2	**5a**	95
4b	CH_3COOAg	50	3	**5b**	87
4c	CH_3COOAg	50	3	**5c**	79
4d	$Hg(OAc)_2$	20	0.1	**5d**	93

a) Starting material (0.25 mmol) in 2 ml of methanol.
b) Isolated yield.

A thiol ester is known to react with an alcohol in the presence of soft metal cations to afford the corresponding ester or lactone,[7] and also a selenol ester was demonstrated to serve as active acyl-transfer agent in the presence of copper(I) or mercury(II).[5-6] However, no example of intramolecular C–N bound formation with soft metal cations has been reported. Thus, it is noteworthy that this novel metal ion promoted reaction can afford cyclic guanidines in good yield under very simple and mild conditions and will be useful for constructing a variety of nitrogen heterocycles.

Experimental

The melting points for the samples were determined with a Mitamura hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu, IR-27G grating IR spectrometer. ^{1}H NMR spectra were determined on a JNM-FX-100 spectrometer. Chemical shifts are reported in δ values relative to Me_4Si as a standard. The physical properties for samples in the experimental section are presented in Table 1.

N-[3-(1-Benzyl-4-piperidinylamino) phenylmethyl]-N'-cyano-S-methylisothiourea (4a). A solution of 1-benzyl-4-[2-(aminomethyl)anilino]piperidine[8] (**3a**, 1.0 g, 3.4 mmol), dimethyl dithiocarboimidate[9] (**6**, 0.59 g, 4 mmol), and triethylamine (0.5 g, 4.9 mmol) in 15 ml of EtOH was stirred for 2 h and concentrated under reduced pressure. The residue was triturated with 2-propanol. The crystals were collected by filtration and recrystallized from EtOH to give 1.4 g (92%) of **4a**. Found: C, 67.37; H, 6.98; N, 17.92%. Calcd for $C_{22}H_{27}N_5S$: C, 67.14; H, 6.91; N, 17.92%.

N-[2-(1-Benzyl-4-piperidinylamino) phenylmethyl]-N'-methoxycarbonyl-S-methylisothiourea (4b). Similarly **3a** (1.0 g, 3.4 mmol) was reacted with **7**[10] (0.68 g, 3.8 mmol) in the presence of triethylamine (0.5 g, 4.9 mmol) in 10 ml of EtOH. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel with $CHCl_3$–MeOH, 30 : 1. Pure **4b** was obtained in 85% yield as an oil. Found: C, 64.72; H, 7.12; N, 12.94%. Calcd for $C_{23}H_{30}N_4O_2S$: C, 64.76; H, 7.09; N, 13.13%.

N-[2-(1-Ethoxycarbonyl-4-piperidinylamino)phenyl]-N'-cyano-S-methylisothiourea (4d). A solution of 1-ethoxycarbonyl-4-(2-aminoanilino)piperidine[11] (**3b**, 1.5 g, 5.7 mmol), **6** (1.5 g, 5.8 mmol), and DBU (1.5 g, 12.1 mmol) in 20 ml of dioxane was heated at 80 °C for 12 h and concentrated. The residue was extracted with ethyl actate and the extract was washed successively with 0.3 mol dm^{-3} acetic acid, 0.57 mol dm^{-3} hydrochloric acid and water. After being dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by silica-gel chromatography using $CHCl_3$–MeOH, 50 : 1 as eluent to afford 0.93 g (45%) of **4d**. An analytical sample was recrystallized from 2-propanol. Found: C, 56.36; H, 6.44; N, 19.19%. Calcd for $C_{17}H_{23}N_5O_2S$: C, 56.49; H, 6.41; N, 19.38%.

1-(1-Benzyl-4-piperidinyl)-2-cyanoimino-1,2,3,4-tetrahydroquinazoline (5a). A mixture of **4a** (973 mg, 2.5 mmol) and silver acetate (450 mg, 2.7 mmol) in 10 ml of MeOH was heated at 50 °C for 5 h and filtered through Celite. The filtrate was concentrated. The residue was dissolved in water, basified with 1 mol dm^{-3} NaOH, and extracted with $CHCl_3$. The extract was washed with aqueous NaCl and water, and dried over Na_2SO_4. Removal of the solvent gave essentially pure **5a** (777 mg, 90%). An analytical sample was recrystallized from 2-propanol. Found: C, 73.09; H, 6.77; N, 20.24%. Calcd for $C_{21}H_{23}N_5$: C, 73.01; H, 6.71; N, 20.28%.

1-(1-Benzyl-4-piperidinyl)-2-methoxycarbonylimino-1,2,3,4-tetrahydroquinazoline (5b). Similar reaction as described for **5a** was repeated by using **4b** (1.29 g, 3 mmol) and silver acetate (0.6 g, 3.6 mmol) in 20 ml of MeOH afforded 990 mg (87%) of **5b**. An analytical sample was recrystallized from AcOEt–hexane. Found: C, 69.76; H, 6.92; N, 14.77%. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.81; H, 6.92; N, 14.81%.

2-Cyanoimino-3-(1-ethoxycarbonyl-4-piperidinyl)-2,3-dihydro-1H-benzimidazole (5d). A solution of **4d** (600 mg, 1.66 mmol) and mercury(II) acetate (535 mg, 1.68 mmol) in 10 ml of MeOH was stirred at room temperature for 1 h and concentrated. The residue was dissolved in $CHCl_3$ and the solution was washed with aqueous NaCl and water. The organic layer was separated and filtered through Celite. The filtrate was dried over Na_2SO_4 and concentrated. The residue almost pure **5d** (485 mg, 93%). An analytical sample was recrystallized from 2-propanol. Found: C, 61.54; H, 6.11; N, 22.18%. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.32; H, 6.11; N, 22.35%.

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