Low-Valent Titanium Induced Reductive Cyclization of Nitriles to Symmetrically Substituted Tetraalkylpyrazines

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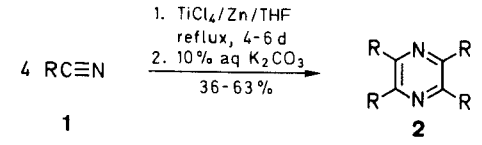
Reductive cyclization of nitriles **1** induced by titanium tetrachloride/zinc provides an efficient general synthesis of symmetrically substituted tetraalkylpyrazines **2**.

Low-valent titanium is an effective tool for reductive coupling of aldehydes and ketones to olefins.[1] A variety of other compounds, such as benzylic and allylic alcohols,[2] trihalomethylarenes,[3] carboxylic acids,[4] and imines[5] can also be coupled. However, the reaction of low-valent titanium with nitriles has not been reported in the literature. We now describe a novel synthesis of symmetrically substituted tetraalkylpyrazines **2** using a reductive cyclization of four nitrile entities by titanium tetrachloride/zinc in modest to good yields.



1, 2	R	1, 2	R
a	CH_3	**f**	n-C_5H_{11}
b	Et	**g**	n-C_6H_{13}
c	Pr	**h**	$PhCH_2$
d	Bu	**i**	4-$ClC_6H_4CH_2$
e	i-Bu	**j**	3-$CH_3$4-$MeOC_6H_3CH_2CH_2$

The results summarized in the Table show that the reaction is general and is especially useful for the preparation of symmetrical tetra substituted pyrazines, which are otherwise not easily accessible. The value of this method is illustrated by the simple synthesis of tetramethyl pyrazaine (**2a**), used as a flavor component in foodstuffs. However, the reaction of the above reagent with aromatic nitriles was not very successful and gave the corresponding symmetrically substituted tetraarylpyrazines in less than 10% yield.

IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. ^{1}H-NMR were obtained on a JMN FX-90Q spectrometer and ^{13}C-NMR on a ZAB-HS spectrometer.

Pyrazines 2; General Procedure:

$TiCl_4$ (4.4 mL, 40 mmol) is added dropwise using a syringe to a stirred suspension of Zn powder (5.24 g, 80 mmol) in freshly distilled dry THF (70 mL) at r.t. under an Ar atmosphere. After the completion of addition, the mixture is refluxed for 1 h. The suspen-

Table. Tetra Substituted Pyrazines **2** Prepared

Product	Yield[a] (%)	bp (°C)/ Torr or mp (°C) (solvent)	Molecular Formula[b] or Lit. Data	IR (KBr or neat) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (M^+)
2a	44	82–84 (cyclohexane)	mp 85–86[6]	2950, 1410, 900, 800	2.33 (s, CH_3)	–	
2b	63	102/10	bp 132–138/ 28[7]	2950, 1460, 1410, 800	1.28 (t, 12H, J = 8.0, CH_3), 2.79 (q, 8H, J = 8.0, CH_2)	12.3, 26.1, 151.0	–
2c	60	64/4	$C_{16}H_{28}N_2$ (248.5)	2950, 1455, 1409, 1376	0.99 (t, 12H, J = 7.7, CH_3), 1.52–1.93 (m, 8H, $CH_3C\underline{H}_2$), 2.73 (t, 8H, J = 8.6, CH_2)	14.1, 22.5, 36.0, 151.1	248
2d	53	160/2.5	$C_{20}H_{36}N_2$ (304.6)	2950, 2780, 1465, 1415	0.95 (m, 12H, CH_3), 1.20–1.90 (m, 16H, $CH_3C\underline{H}_2C\underline{H}_2$), 2.75 (t, 8H, J = 8.6, CH_2)	14.0, 22.5, 31.5, 33.5, 151.2	304
2e	61	130/2.5	$C_{20}H_{36}N_2$ (304.6)	2960, 2800, 1455, 1410, 670	0.92 (d, 24H, J = 8.1, CH_3), 1.50–1.92 (m, 4H, CH), 2.65 (d, 8H, J = 7.7, CH_2)	22.5, 28.2, 42.2, 150.4	304
2f	48	130/0.2	$C_{24}H_{44}N_2$ (360.7)	2950, 2750, 1465, 1415, 660	0.91 (m, 12H, CH_3), 1.10–1.43 (m, 16H, $CH_3C\underline{H}_2C\underline{H}_2$), 1.50–1.90 (m, 8H, $CH_3CH_2CH_2C\underline{H}_2$), 2.70 (t, 8H, J = 8.6, CH_2)	13.8, 22.5, 28.0, 32.0, 34.0, 151.0	360
2g	52	160/0.3	$C_{28}H_{52}N_2$ (416.8)	2900, 2700, 1580, 1410, 668	0.90 (m, 12H, CH_3), 1.10–1.78 (m, 24H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.20–2.45 (m, 8H, $BuC\underline{H}_2$), 2.72 (t, J = 8.6, CH_2)	14.1, 22.5, 29.0, 29.5, 31.8, 34.0, 151.0	416
2h	46	102–104 (cyclohexane)	$C_{32}H_{28}N_2$ (440.6)	3030, 2950, 1600, 1490, 710, 670	4.10 (s, 8H, CH_2), 7.18 (s, 20H$_{arom}$)	40.5, 126.4, 128.5, 128.9, 138.7, 151.2	440
2i	39	157–159 (PE)[c]	$C_{32}H_{24}Cl_4N_2$ (578.4)	1590, 1430, 1395, 1090, 820, 800, 790, 750	4.05 (s, 8H, CH_2), 6.93–7.25 (m, 16H$_{arom}$)	39.7, 128.7, 130.2, 132.5, 136.8, 150.9	576
2j	36	118–120 (PE)[c]	$C_{44}H_{52}N_2O_4$ (672.9)	1610, 1510, 1400, 1250, 880, 810, 750	2.16 (s, 12H, CH_3), 2.85–3.01 (m, 16H, CH_2CH_2), 3.80 (s, 12H, CH_3O), 6.65–7.24 (m, 12H$_{arom}$)	16.2, 34.3, 36.1, 55.6, 110.3, 126.6, 131.0, 133.8, 150.9, 156.3	672

[a] Yield of pure isolated product.
[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.20, N ±0.25.
[c] PE = Petroleum ether (bp 60–90 °C).

sion of the low-valent titanium reagent formed is cooled to r.t. and the nitrile **1** (40 mmol) is added carefully. Reflux is continued with stirring for 4–6 d under an Ar atmosphere, then most of the solvent is removed by vacuum, the residue is cooled, poured into 10% aq K_2CO_3 (400 mL), and extracted with $CHCl_3$ (3 × 150 mL). The combined $CHCl_3$ extracts are washed with water (3 × 40 mL), dried (Na_2SO_4), and the solvent removed to give the pyrazines **2**, which are further purified by recrystallization, distillation *in vacuo* or column chromatography on silica gel (eluent: CH_2Cl_2/petroleum ether (bp 60–90 °C), 2:1) (Table).

Financial support of this research from the National Natural Science Foundation of China is gratefully acknowledged.

Received: 12 July 1989; revised: 4 January 1990

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