ONE STEP SYNTHESIS OF BICYCLOALKAPYRAZINES USING DINITRILES WITH LOW–VALENT TITANIUM

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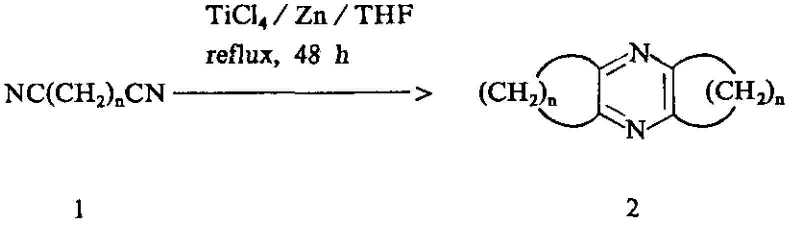
Abstract— Preparative methods of obtaining bicycloalkapyrazines (**2**) by the low–valent titanium induced reductive cyclization of dinitriles (**1**), and for obtaining bi(azacycloalka)pyrazines (**5**) from *N,N*–bis(2–cyanoethyl)–aromatics amines (**4**) are presented.

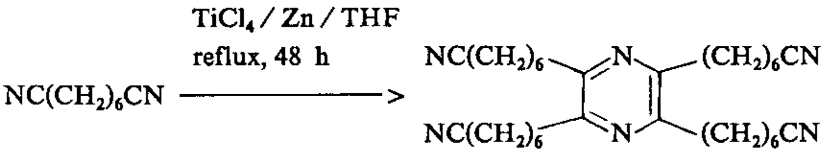
In the hope of widening the scope of application of low–valent titanium reagent in organic synthesis,[1] we investigated the reductive coupling reaction of nitriles and we have recently reported that aliphatic nitriles can be reductively coupled to give pyrazines by treatment with $TiCl_4$–Zn.[2] Now we report that the reductive coupling of aliphatic dinitriles with the same reagent gives bicycloalkapyrazines (**2**).

Treatment of glutaronitrile (**1a**), adiponitrile (**1b**), and pimelonitrile (**1c**) with $TiCl_4$–Zn in THF at reflux temperature afforded the corresponding bicycloalkapyrazines (**2a**), (**2b**), and (**2c**), respectively. Cycloalkapyrazines are important flavor constituents of a variety of roasted foods.[3]



n= 3, 4, 5

However, treatment of suberonitrile (**1d**) with using the same reaction system, afforded the tetrakis(ω–cyanoheptyl)pyrazine (**3**). Attempts to prepare the bicycloalkapyrazine (2) (n = 1) by reductive cyclization of malononitrile was unsuccessful.



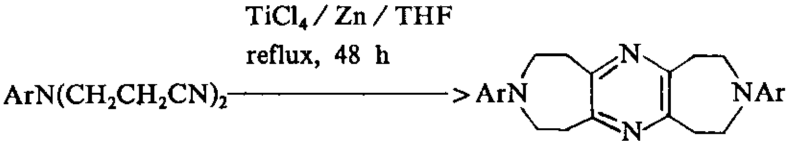
1d 3

Table 1. Bicycloalkapyrazines (2, 3)

Product	Yield (%)	mp(℃) (solvent)^a	C H N Found / Cacld	ir(KBr) ν(cm^{-1})	^{1}H–nmr(CDCl$_3$–TMS) δ(ppm)	ms(EI) m / z(M$^+$)
2a	48	83–85	74.93 7.38 17.90 74.97 7.55 17.48	2953, 1467, 1428, 1016, 905, 839	2.13–2.75(m, 4H, 2CH$_2$), 2.95(t, J=8.0 Hz, 8H, ring–CH$_2$)	160
2b	51	107–108 106–108^4		2900, 1450, 1390, 1190, 870, 810	1.74–2.25(m, 8H, 4CH$_2$), 2.70–3.13(m, 8H, ring–CH$_2$)	
2c	26	136–138	77.83 9.50 12.83 77.74 9.32 12.95	2985, 1452, 1410, 956, 895, 830	1.40–2.00(m, 12H, 6CH$_2$), 2.73–3.17(m, 8H, ring–CH$_2$)	216
3	21	65–66 (EtOH)	74.15 9.41 16.49 74.38 9.36 16.26	2933, 2240, 1467, 1068, 728	1.53–2.03(m, 32H, 16CH$_2$), 2.30(t, J=8.0 Hz, 8H, 4CH$_2$CN), 2.72(t, J= 6.0 Hz, 8H, ring–CH$_2$)	516

a Recrystallization from cyclohexane.

On the other hand, treatment of N,N–bis(2–cyanoethyl)aromatic amine (**4a–4e**) with the same reagent also afforded the bi(azacycloalka)pyrazine (**5a–5e**).



4 5

4,5	Ar
a	C_6H_5
b	o–$CH_3C_6H_4$
c	m–$CH_3C_6H_4$
d	p–$CH_3C_6H_4$
e	p–$CH_3OC_6H_4$

Table 2. Bi(azacycloalka)pyrazines (5)

Product	Yield (%)	mp(℃) (EtOH)	C	H	N	ir(KBr) ν(cm^{-1})	^{1}H–nmr($CDCl_3$–TMS) δ(ppm)	ms(EI) m / z(M$^+$)
			Found / Cacld					
5a	32	190–192	77.55 77.80	7.31 7.07	14.88 15.12	3064, 2966, 1467, 1402, 741, 682	3.05–3.35(m, 8H, $4CH_2$), 3.60–3.85(m, 8H, $4NCH_2$), 6.65–7.38(m, $10H_{arom}$)	370
5b	28	178–180	78.19 78.34	7.65 7.58	14.01 14.06	3031, 2830, 1440, 950, 760, 725	2.37(s, 6H, $2CH_3$), 3.02–3.48(m, 16H, $8CH_2$), 6.73–7.27(m, $8H_{arom}$)	398
5c	33	226–227	78.35 78.34	7.53 7.58	14.04 14.06	3031, 2940, 1446, 1410, 924, 839, 761, 689	2.32(s, 6H, $2CH_3$), 3.01–3.32(m, 8H, $4CH_2$), 3.60–3.93(m, 8H, $4NCH_2$), 6.57–7.27(m, $8H_{arom}$)	398
5d	30	206–207	78.40 78.34	7.61 7.58	13.68 14.06	3025, 2953, 1460, 1414, 937, 894, 801	2.27(s, 6H, $2CH_3$), 3.30–3.33(m, 8H, $4CH_2$), 3.58–3.86(m, 8H, $4NCH_2$), 6.83–7.30(m, $8H_{arom}$)	398
5e	27	214–215	72.34 72.53	7.08 7.02	12.53 13.01	3031, 2900, 1470, 1415, 940, 815, 740	3.05–3.33(m, 8H, $4CH_2$), 3.50–3.70(m, 8H, $4NCH_2$), 3.77(s, 6H, $2OCH_3$), 6.86–7.18(m, $8H_{arom}$)	430

EXPERIMENTAL

Ir spectra were recorded on Nicolet FT–5DX spectrophotometer, ^{1}H–nmr were obtained on JNM–PMX 60SI spectrometer, ms were obtained on ZAB–HS spectrometer.

Pyrazines; General Procedure: $TiCl_4$ (3.3 ml, 30 mmol) was added dropwise to a stirred suspension of Zn power (3.90 g, 60 mmol) in freshly distilled dry THF (70 ml) at room temperature under an Ar atmosphere. After the completion of addition, the mixture was refluxed for 1 h under an Ar atmosphere. The suspension of the low–valent titanium reagent formed was cooled to room temperature and the dinitrile (15 mmol) was added carefully. Reflux was continued with stirring for 48 h under an Ar atmosphere, then most of the solvent was removed by vacuum, the residue was cooled, poured into 10% K_2CO_3 (300 ml), and extracted with $CHCl_3$ (3x150 ml). The conbined extracts were washed with water (3x40 ml), dried

(Na_2SO_4), and the solvent was removed to give the pyrazines, which were further purified by column chromatography on silica gel(eluent: ethyl acetate / petroleum ether(60–90°C) (1:3))(Tables 1,2).

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