

Proceeding Paper

Multiple Pathways in Cp₂TiCl₂-catalyzed Reaction of Tetraalkyl-substituted Pyrazines with EtAlCl₂ and Mg[†]

 Mariya G. Shaibakova ¹, Nikita A. Rikhter ¹, Leisan K. Dil'mukhametova ¹, Ilfir R. Ramazanov ^{1,*}

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, 450075 Ufa, Russia

* Correspondence: shaibakovamg@mail.ru; Tel.: +7-90-5357-7794

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Abstract: There exist a number of classical methods for the synthesis of substituted pyrazines. Among this variety of reactions, the synthesis of substituted pyrazines from nitriles stands out neither in the number of known examples nor in product yields. However, the one-stage character of the transformation, together with the uncertainty of its mechanism, aroused our interest in this catalytic reaction. Here we report the successful implementation of Cp₂TiCl₂-catalyzed reaction of aliphatic nitriles with EtAlCl₂ and Mg, which led to the selective preparation of 2,3,5,6-tetraalkyl-substituted pyrazines, 2,4,5-trisubstituted-1*H*-imidazole or 2-aminocyclopent-1-ene-carbonitrile depending on reaction conditions and substituents.

Keywords: Metal complex catalysis; Dichlorobis(η⁵-cyclopentadienyl)titanium; Ethylaluminum dichloride; Nitriles; Tetrasubstituted pyrazines

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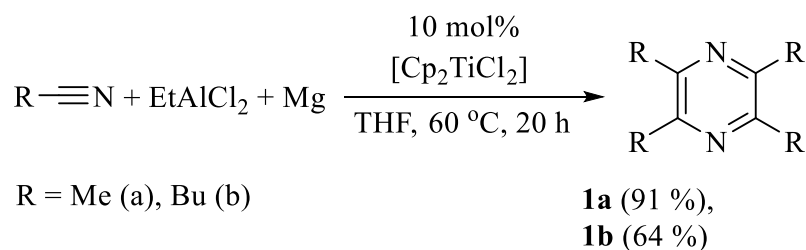
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1. Introduction

There exist a number of classical methods for the synthesis of substituted pyrazines via homocondensation of α-aminoketones and α-aminoaldehydes, co-condensation of ethylenediamines with 1,2-diketones, the reaction of 2-nitrooxiranes with ammonia, the reaction of aryl-substituted α-hydroxyketones with ammonium acetate in acetic acid, the cyclodimerization reactions of azirines, as well as cyclizations of *N,N'*-dibenzylidene derivatives [1–8] and others [9,10]. Among this variety of reactions, the synthesis of substituted pyrazines from nitriles stands out neither in the number of known examples nor in product yields. Indeed, only three examples of such reactions are known [11–13]. However, the one-stage character of the transformation, together with the uncertainty of its mechanism, aroused our interest in this catalytic reaction. We recently reported a new efficient method for the synthesis of 2,3,5,6-tetraaryl-substituted pyrazines by the reaction of aromatic nitriles with EtAlCl₂ in the presence of Mg and the catalyst Cp₂TiCl₂ ([ArCN] : [EtAlCl₂] : [Mg] : [Cp₂TiCl₂] = 4 : 2 : 4 : 0.1, THF, 0 °C, 8 h) [13]. Aliphatic nitriles were not converted under these reaction conditions. Now, we found conditions for the production of alkyl-substituted pyrazines Here we report the successful implementation of Cp₂TiCl₂-catalyzed reaction of aliphatic nitriles with EtAlCl₂ and Mg, which led to the selective preparation of 2,3,5,6-tetraalkyl-substituted pyrazines.

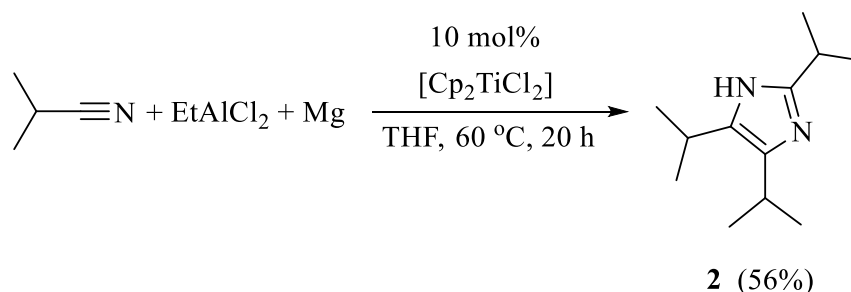
2. Results and Discussion

It was found that the reaction of aliphatic nitriles 1a-d with 0.5 equivalents of EtAlCl₂ and 0.5 equivalents of Mg in a THF solution in the presence of catalytic amounts of Cp₂TiCl₂ (0.025 equivalents) at 60 °C gave 2,3,5,6-tetraalkyl-substituted pyrazines 1a,b in 60–91% yield based on the starting alkyl nitrile.

**Scheme 1.**

To select the most active and selective catalyst in this reaction, we tested a number of Ti, Zr, Hf, Ni, Pd complexes. From the tested catalysts, Cp₂TiCl₂ exhibited the greatest catalytic activity and selectivity.

Surprisingly, when isobutyronitrile was used as the alkylnitrile, 2,4,5-triisopropyl-1*H*-imidazole **2** was obtained in 56% yield instead of the expected tetrasubstituted pyrazine (Scheme 2).

**Scheme 2.**

It seems that there are two different reaction pathways, one leading to the formation of pyrazines and the other to imidazoles. It is known that the homocoupling of nitriles with the use of the Rosenthal reagent proceeds as C-C coupling or as N-C coupling. Based on the fact that the reaction with an alkylnitrile having a bulky substituent proceeded along a different route, it can be assumed that in this case the interaction between the nitrile molecules proceeds as N-C coupling. At this stage of the study, we find it difficult to formulate in detail the mechanism of imidazole formation in the reaction under study.

3. Conclusion

In conclusion, we have developed the one-pot catalytic synthesis of tetrasubstituted pyrazines from alkyl-substituted nitriles and EtAlCl₂ in the presence of metallic Mg and Cp₂TiCl₂ catalyst in good yield.

4. Experimental Part

General. Chromatographic analysis was performed on a Shimadzu GC-9A instrument using a 2000×2 mm column, the SE-30 (5 %) stationary phase on Chromaton N-AW-HMDS (0.125–0.160 mm), helium carrier gas (30 mL/min), temperature programming from 50 to 300 °C at a 8 °C/min rate. The ¹H, ¹³C NMR spectra were measured in CDCl₃ on a Bruker Avance-400 spectrometer (100.62 MHz for ¹³C, 400.00 MHz for ¹H). Elemental analysis was performed using a Carlo-Erba CHN 1106 elemental analyser. Mass spectra were obtained on a Finnigan 4021 instrument. TLC was performed on Silufol UV-254 plates with hexane–ethyl acetate (100:3–50 mixture as the eluent and I₂ or anise developer for visualization. For column chromatography, Acros silica gel (0.060–0.200 mm) was used. Reactions with organometallic compounds were performed in a dry

argon flow. The solvents were dried and distilled immediately prior to use. Commercially available nitriles, Cp_2TiCl_2 , Mg and EtAlCl_2 were used.

Experimental Procedures. A 50 mL glass reactor equipped with a magnetic stirrer under a dry argon atmosphere at 0 °C, was charged under stirring with THF (60 mL), EtAlCl_2 (40 mmol), Mg (40 mmol, powdered) and the Cp_2TiCl_2 catalyst (1.0 mmol). After 1 h, organic nitrile (10 mmol) was added. The temperature was raised to 60–65 °C and the mixture stirred for an additional 20 h. The mixture was cooled under an argon stream to 0 °C. After the addition of Et_2O (30 mL), the mixture was quenched with a 10% aqueous solution of NaOH (10 mL), the organic layer separated, and the aqueous layer extracted with Et_2O (3 x 25 mL). The combined organics were dried over MgSO_4 . The products were isolated by column chromatography.

compound 1a was isolated by column chromatography (hexanes/ EtOAc = 100:5), (hexanes→hexanes/ EtOAc 100:1→100:5) provided 2,3,5,6-tetramethylpyrazine as a white solid (309 mg, (2.27mmol), 91 %). Mp 84-86 °C. IR (film) 2963, 1463, 1427, 915, 825. cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.71 (s, 12 H); ^{13}C NMR (400 MHz, CDCl_3) δ 148.17, 21.28. MS (EI): m/z (%) = 136 $[\text{M}]^+$.

compound 2 was isolated by column chromatography (hexanes/ EtOAc = 2:1) provided 2,4,5-triisopropyl-1H-imidazole as a white solid (489 mg, (1.61mmol) 64 %). Mp 138-139 °C. R_f 0.63. IR (film) 2964, 2872, 1666, 1530, 1305, 1104, 876. cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.15-1.24 (m, 18 H), 2.90-3.02 (m, 2 H), 8.21(s, 1 H). ^{13}C NMR (400 MHz, CDCl_3) δ 161.20, 150.51, 133.78, 28.31, 25.30, 22.98, 21.84. (EI): m/z (%) = 194 $[\text{M}]^+$. Anal. calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2$, (%): C, 74.17; H, 11.41; N, 14.42. Found, %: C, 73.9; H, 11.3; N, 14.2.

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Conflicts of Interest: The authors declare no conflict of interest.

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