

Multiple Pathways in Cp_2TiCl_2 —Catalyzed Reaction of Tetraalkyl-Substituted Pyrazines with EtAlCl_2 and Mg [†]

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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 does not stand out in either the number of known examples or in product yield. 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 the Cp_2TiCl_2 -catalyzed reaction of aliphatic nitriles with EtAlCl_2 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(η^5 -cyclopentadienyl)titanium; ethylaluminum dichloride; nitriles; tetrasubstituted pyrazines



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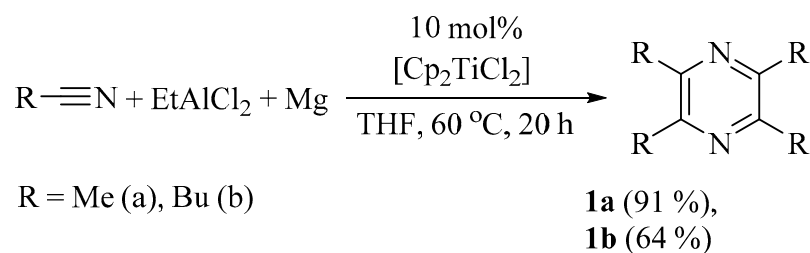
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1. Introduction

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 does not stand out in either the number of known examples or in product yield. 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 EtAlCl_2 in the presence of Mg and the catalyst Cp_2TiCl_2 ($[\text{ArCN}]:[\text{EtAlCl}_2]:[\text{Mg}]:[\text{Cp}_2\text{TiCl}_2] = 4:2:4:0.1$, THF, 0 °C, 8 h) [14]. Aliphatic nitriles were not converted under these reaction conditions. Now, we have found conditions for the production of alkyl-substituted pyrazines. Here, we report the successful implementation of a Cp_2TiCl_2 -catalyzed reaction of aliphatic nitriles with EtAlCl_2 and Mg , which led to the selective preparation of 2,3,5,6-tetraalkyl-substituted pyrazines.

2. Results and Discussion

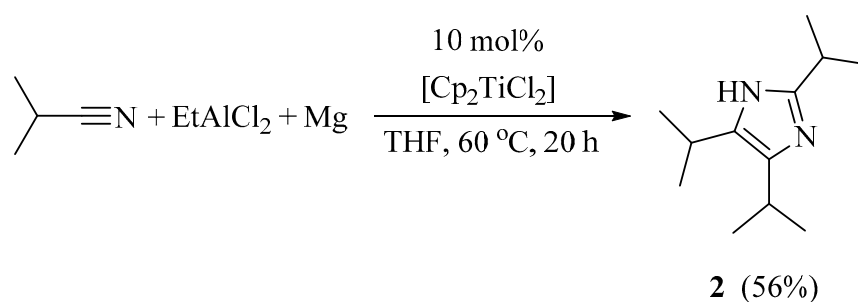
It was found that the reaction of aliphatic nitriles **1a–d** with 0.5 equivalents of EtAlCl_2 and 0.5 equivalents of Mg in a THF (tetrahydrofuran) solution in the presence of catalytic amounts of Cp_2TiCl_2 (0.025 equivalents) at 60 °C gave 2,3,5,6-tetraalkyl-substituted pyrazines **1a,b** with 60–91% yield based on the starting alkyl nitrile (Scheme 1).



Scheme 1. Synthes of 2,3,5,6-tetraalkyl-substituted pyrazines from aliphatic nitriles.

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, Cp_2TiCl_2 exhibited the greatest catalytic activity and selectivity.

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



Scheme 2. Synthes of 2,4,5-triisopropyl-1H-imidazole **2** from isobutyronitrile.

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 a C-C coupling or as a 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 would proceed as a 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. Conclusions

In conclusion, we have developed the one-pot catalytic synthesis of tetrasubstituted pyrazines from alkyl-substituted nitriles and $EtAlCl_2$ in the presence of metallic Mg and Cp_2TiCl_2 catalyst in good yield.

4. Experimental Section

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 , ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker Avance-400 spectrometer (100.62 MHz for ^{13}C , 400.00 MHz for 1H). Elemental analysis was performed using a Carlo-Erba CHN 1106 elemental analyzer. 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 I_2 ore 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), EtAlCl₂ (40 mmol), Mg (40 mmol, powdered) and the Cp₂TiCl₂ 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 Et₂O (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 Et₂O (3 × 25 mL). The combined organics were dried over MgSO₄. The products were isolated by column chromatography.

Compound **1a** was isolated by column chromatography (hexanes/EtOAc = 100:5), (hexanes/EtOAc 100:5) provided 2,3,5,6-tetramethylpyrazine as a white solid (309 mg, (2.27 mmol), 91%). Mp 84–86 °C. IR (film) 2963, 1463, 1427, 915, 825. cm^{−1}. ¹H NMR (400 MHz, CDCl₃) δ 2.71 (s, 12 H); ¹³C NMR (400 MHz, CDCl₃) δ 148.17, 21.28. MS (EI): *m/z* (%) = 136 [M]⁺.

Compound **2** was isolated by column chromatography (hexanes/EtOAc = 2:1) provided 2,4,5-triisopropyl-1*H*-imidazole as a white solid (489 mg, (1.61 mmol) 64%). Mp 138–139 °C. R_f 0.63. IR (film) 2964, 2872, 1666, 1530, 1305, 1104, 876. cm^{−1}. ¹H NMR (400 MHz, CDCl₃) δ 1.15–1.24 (m, 18 H), 2.90–3.02 (m, 2 H), 8.21 (s, 1 H). ¹³C NMR (400 MHz, CDCl₃) δ 161.20, 150.51, 133.78, 28.31, 25.30, 22.98, 21.84. (EI): *m/z* (%) = 194 [M]⁺. Anal. calcd for C₁₂H₂₂N₂, (%): C, 74.17; H, 11.41; N, 14.42. Found, %: C, 73.9; H, 11.3; N, 14.2.

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