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Technical Notes

Formation of 2-Trifluoromethylphenyl Grignard Reagent via Magnesium−Halogen Exchange: Process Safety Evaluation and Concentration Effect

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Abstract:

The thermal stability profile for a solution of 2-trifluoromethylphenyl magnesium chloride at 1.5 M concentration in THF was determined using an Advanced Reactive System Screening Tool (ARSST). The solution generated by employing Knochel's magnesium−halogen exchange protocol showed highly exothermic decomposition. The decomposition begins at a low-onset temperature accompanied by a rapid temperature and pressure rise. Analysis of the decomposition mixture revealed the destruction of trifluoromethyl group and formation of fluoride ion. This decomposition profile was substantially attenuated by reducing the concentration of the solution to 0.5−0.6 M. Thus, it is strongly recommended that selecting an appropriate concentration for the reagent based on calorimetric evaluation should be included with procedural and engineering controls when considering any strategy for safe scale-up of trifluoromethyl-substituted phenyl Grignard solutions.

Introduction

The trifluoromethyl-substituted arene moiety is being exploited with increasing frequency for the design of pharmaceutical and agrochemical agents.[1] The desire to evaluate the unique properties of these compounds in biological systems has stimulated the search for practical synthetic methods to prepare them. Trifluoromethyl-substituted phenyl Grignard reagents are versatile intermediates that could potentially satisfy the requirements. However, the preparation of these intermediates from a suitable aryl halide by the traditional method using magnesium metal is extremely dangerous. Several severe explosions have been reported.[2] For example, an accident during the preparation of 4-trifluoromethylphenyl magnesium chloride on a commercial scale resulted in loss of life and destruction of a chemical plant.[3] Pfizer reported a severe decomposition during the formation of 3-trifluoromethylphenyl magnesium bromide causing extensive damage to a laboratory.[4] It was believed that the severe decomposition was initiated by highly active magnesium particles generated in the reaction.[2] This important process safety issue has hampered the utility of trifluoromethyl-substituted phenyl Grignard reagents in large-scale organic synthesis.

In the last 10 years, Knochel and co-workers have developed an attractive method for generating aryl Grignard reagents by employing an alkyl Grignard reagent such as *i*PrMgCl to promote metal−halogen exchange.[5] This method enables the transformation of many aromatic iodides and bromides into aromatic Grignard reagents at or below room temperature. By contrast, the traditional method mediated by magnesium metal often requires heating and initiation to avoid a dangerous induction period. From the process safety point of view, the Knochel methodology would seem to possess attractive characteristics for large-scale preparation. Further encouragement for the use of Knochel's method in an industrial context was offered by Leazer and co-workers at Merck who described a safer process for 3,5-bis(trifluoromethyl)phenyl Grignard reagent from 3,5-bis(trifluoromethyl)bromobenzene and *i*PrMgBr.[6] The Merck scientists examined the stability of various trifluoromethyl-substituted phenyl Grignard reagents using Differential Thermal Analysis (DTA) and a Reactive System Screening Tool (RSST). They concluded Knochel's method was safer for the preparation of these reagents than the traditional method with magnesium metal. Indeed the testing showed no exothermic decomposition from Grignard solutions prepared with Knochel's

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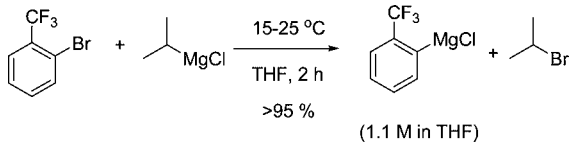
Scheme 1. **Formation of 2-trifluoromethylphenyl Grignard reagent by magnesium−bromide exchange**



method, although no information about concentration was mentioned in the paper.

Considering the inherently safer features of Knochel's method and the results of the Leazer investigation, we were optimistic that employing 2-trifluoromethylphenyl Grignard reagent would be an ideal strategy to accomplish one of our recent process development challenges. Thus, by using Knochel's method, 2-bromobenzotrifluoride was converted to 2-trifluoromethylphenyl magnesium chloride solution (~1.1 M) with >95% conversion as illustrated in Scheme 1. Here, we would like to report our studies concerning the exothermic decomposition of this solution at elevated temperature by using adiabatic calorimetry in an Advanced Reactive System Screening Tool (ARSST) and the influence of concentration on this event.

Results and Discussion

A sample (10 mL) of solution prepared as shown in Scheme 1 was transferred under nitrogen atmosphere to the reaction cell in a closed 350-mL ARSST containment vessel. The purged containment was filled with nitrogen (~300 psig) and subjected to a temperature ramp rate of ~2 °C/min (see Experimental Section for more details). To our surprise, a highly exothermic event was observed with the onset temperature at about 80 °C. The peak rate of temperature rise (d*T*/d*t*) reached 3200 °C/min, and the peak rate of pressure rise (d*P*/d*t*) reached 6000 psi/min (Figure 1). This severe decomposition was in sharp contrast to Leazer's report,[6] where no severe exothermic events were

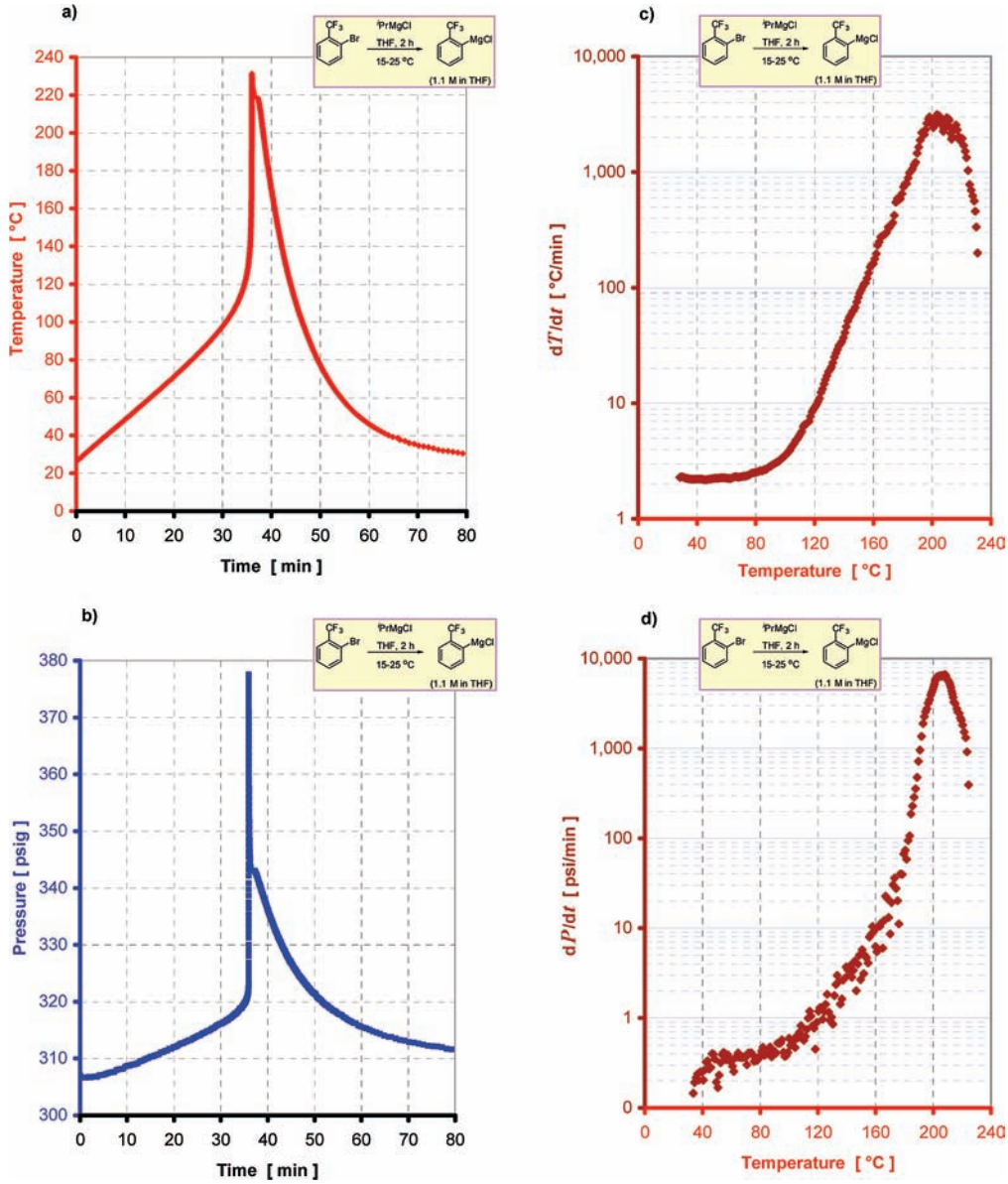
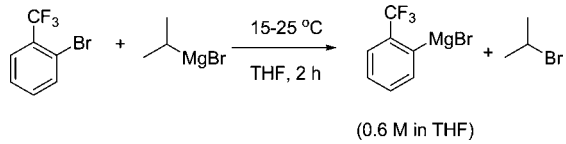


Figure 1. **Formation of 2-trifluoromethylphenyl magnesium chloride (1.1 M). Data from ARSST quasi-adiabatic calorimetry: (a) temperature vs time plot; (b) pressure vs time plot; (c) time derivative of temperature (temperature rise rate) vs temperature plot (log scale); (d) time derivative of pressure (pressure rise rate) vs temperature plot (log scale). Both the heat-up and cool-down portions are shown in (a) and (b). Only the heat-up portion is shown in (c) and (d).**

Scheme 2. **Magnesium−bromide exchange with *i*PrMgBr**



(0.6 M in THF)

observed during both DTA and RSST studies. In order to eliminate the possible involvement of magnesium particles introduced from commercial Grignard reagent, the *i*PrMgCl solution purchased from Sigma-Aldrich was filtered through a 10 μm filter prior to performing the magnesium−halogen exchange. The experimental data once again showed a dramatic decomposition event with similar magnitude. The low decomposition onset temperature (~80 °C) together with very rapid temperature and pressure rise led to a process safety concern for scale-up to pilot-plant batches. Since Leazer et al. employed *i*PrMgBr and not *i*PrMgCl as the reagent for their RSST and DTA studies, we wondered whether this difference could explain the contrast between our respective observations. We thus employed a commercial solution of *i*PrMgBr (0.85−1.0 M) to prepare a solution of 2-trifluoromethylphenyl magnesium bromide solution at ~0.6 M concentration (Scheme 2). The ARSST profile of this solution showed a much milder exothermic decomposition with the onset temperature at about 100 °C, a peak rate of temperature rise at 50 °C/min, and a peak rate of pressure rise at 10 psi/min (Figure 2). Although the concentration of this Grignard reagent (0.6 M) is essentially half that of the aforementioned 2-trifluoromethylphenyl magnesium chloride solution (1.1 M), we found it striking that the differences in both the peak rate of temperature and pressure rise for the decomposition disproportionately large. To distinguish whether the results are due to a counterion effect (Cl vs

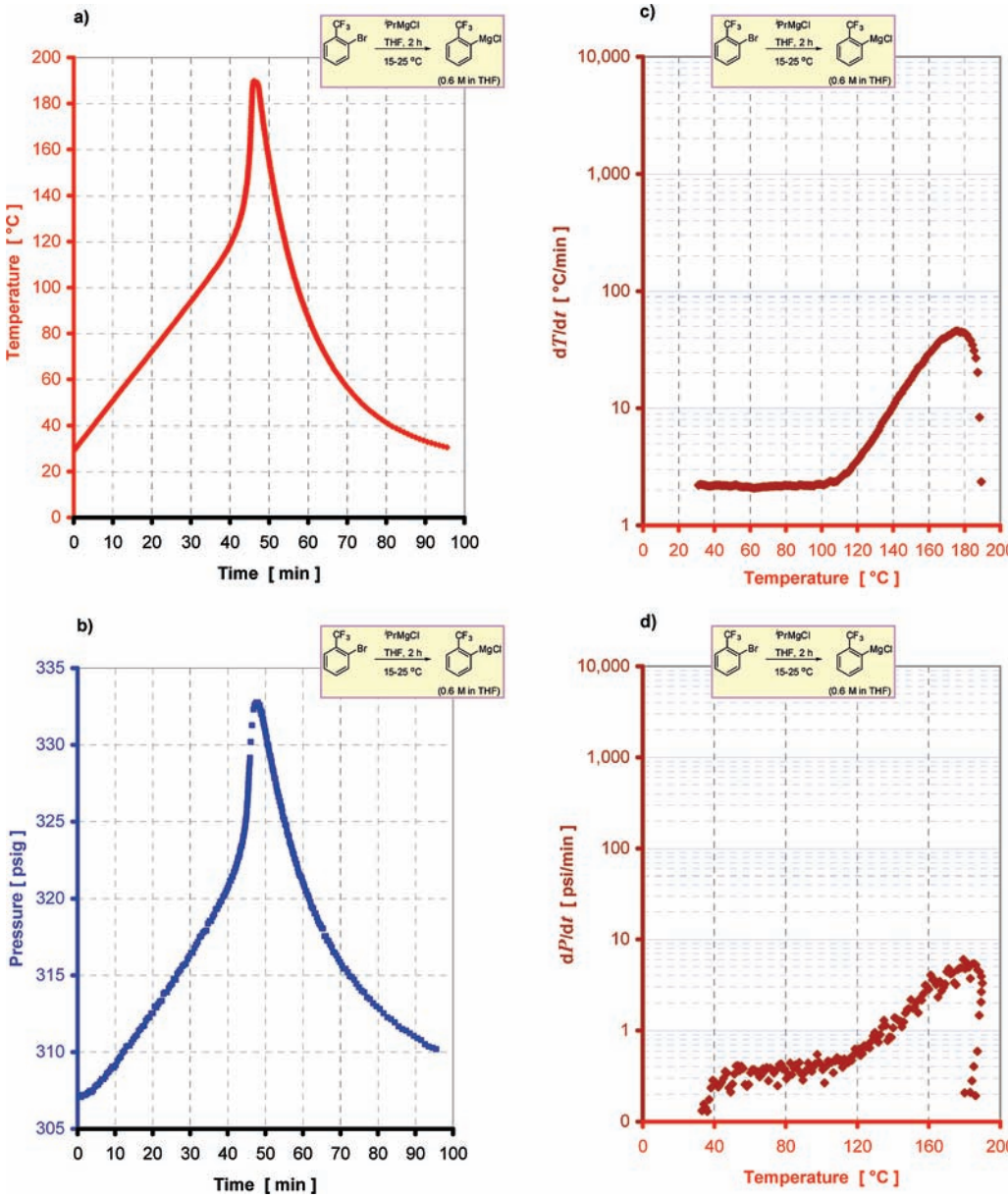
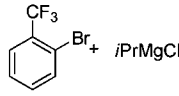
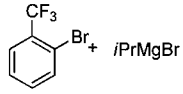
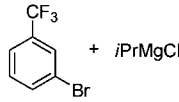
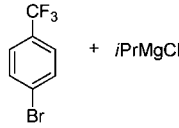
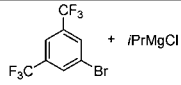


Figure 2. **Formation of 2-trifluoromethylphenyl magnesium chloride (0.6 M). Data from ARSST quasi-adiabatic calorimetry: (a) temperature vs time plot; (b) pressure vs time plot; (c) time derivative of temperature (temperature rise rate) vs temperature plot (log scale); (d) time derivative of pressure (pressure rise rate) vs temperature plot (log scale). Both the heat-up and cool-down portions are shown in (a) and (b). Only the heat-up portion is shown in (c) and (d).**

Table 1. **Data summary from ARSST quasi-adiabatic calorimetry of various trifluoromethyl-substituted phenyl Grignard solutions made with Knochel's method at different concentrations**

Experiment No[a]	Reaction	Concentration of corresponding aryl Grignard reagent (M)	Estimated Onset Temperature (°C)	Peak dT/dt (°C/min)	Peak dP/dt (psi/min)	Estimated Adiabatic Temperature rise $\Delta T_{ad.}$ (°C)
1		1.5	70	15,000	70,000	150
2		1.1	80	3,200	6,000	125
3		0.6	100	50	10	60
4		0.5	100	25	5	50
5		0.75	100	250	60	85
6		0.6	110	50	10	50
7		1.5	100	560	850	125
8		0.5	N/A	7	2	N/A
9[b]		1.5	55	600	1,000	230
10		0.5	N/A	4	1	N/A
11		1.5	80	50	100	95
12		0.5	N/A	5	2	N/A

[a] The reactions were run under nitrogen at 15−25 °C in THF for 2−12 h. Mole ratio of aryl bromide: *i*PrMgBr/*i*PrMgCl = 1:1.05. A 10-mL sample was taken for adiabatic calorimetry experiment. See Experimental Section for details. [b] The mixture is highly exothermic during decomposition as two consecutive decomposition events were observed.

Br) or a concentration effect, a solution of 2-trifluoromethylphenyl magnesium chloride with the same concentration (~0.6 M) was prepared and evaluated by ARSST (Table 1, experiments 3 and 6). The results were similar to those obtained from the 2-trifluoromethylphenyl magnesium bromide solution. This indicates that the decomposition rate is not dependent on the counterions present but on the concentration of the Grignard solution. Table 1 provides additional data that establish the direct relationship between concentration and the severity of decomposition. An extremely exothermic event was seen when the concentration increased to 1.5 M while a Grignard solution at 0.5 M concentration exhibits a greatly subdued decomposition profile (experiment 1 vs 4). A 3-fold reduction in concentration provides a dramatic difference in the onset temperature (100 °C vs 70 °C) and the decomposition rates (peak dT/dt: 25 °C/min vs 15,000 °C/min, peak dP/dt: 5 psi/min vs 70,000 psi/min). This trend was also observed with 3-trifluoromethylphenyl Grignard solution, 4-trifluoromethylphenyl Grignard solution, and 3,5-ditrifluoromethylphenyl Grignard solution, although the relative change in magnitude and onset temperature for the decomposition events varied with substrates. Severe decompositions were observed of all the solutions at a high concentreation (~1.5 M). A significant exothermic activity with two consecutive decomposition events was observed in the thermal profile of 1.5 M 4-trifluoromethylphenyl Grignard solution (see Supporting Information). On the other hand, little or no exothermic activity was seen at 0.5 M concentration.

HPLC analysis of the decomposition products of 2-trifluoromethylphenyl Grignard solution revealed a complex mixture. The ^{19}FNMR spectrum obtained from the mixture displays a wide range of ^{19}F signals (−40 to −110 ppm), suggesting the involvement of the trifluoromethyl group in one or more decomposition pathways. The presence of fluoride ion in the decomposition mixture is substantiated by ion chromatographic analysis. Calculations based on the fluoride ion content and the total fluorine content of the decomposition mixture indicate that nearly one-fourth to one third of organic fluorine has been transformed into ionic fluoride (see Supporting Information).

While these pathways are not easily understood, we speculate that the main energy release could be largely due to the formation of magnesium fluoride species owing to its high lattice energy (the lattice energy of MgF_2 is −2957 kJ/mol).

In summary, we have characterized the effect of concentration on the thermal decomposition of trifluoromethyl-substituted phenyl Grignard solutions generated with Knochel's method using adiabatic calorimetry. The results demonstrate the importance of this factor in gauging the risks involved with the scale-up of these reagents despite the fact that they have been prepared by Knochel's method.[7] It is our hope that the chemical development community will benefit from this information when an assessment is required to determine whether these reagents can play a role at some stage in the development of a biologically active substance containing the trifluoromethyl-substituted arene moiety. A more effective strategy for safe scale-up is possible when the concentration factor is combined with procedural and engineering controls. In our scale-up program, we successfully produced 83 L (50 mol) of 2-trifluoromethylphenyl magnesium bromide solution in THF at 0.6 M concentration.

Experimental Section

General. All reagents were purchased from commercial sources and used without further purifications unless otherwise specified. All reactions and adiabatic calorimetry experiments were performed under N_2 atomosphere. HPLC analysis was performed on an Agilent 1200 series with Halo C8 column; flow rate of 1.3 mL/min; UV detection at 205 and 220 nm; mobile phase of water (0.1% H_3PO_4) and MeCN/THF (95:5, v/v) with gradient composition.

General Procedure for Preparation of Trifluoromethyl-Substituted Aryl Grignard Solution. To a 250-mL three-necked flask equipped with magnetic stirrer and thermometer was charged a solution of *i*PrMgCl (47 mL, 2.0 M, 94 mmol, 1.05 equiv) or *i*PrMgBr (104 mL, 0.9 M, 94 mmol, 1.05 equiv) in THF. To the mixture at ∼15 °C was added neat trifluoromethyl-substituted bromide (89 mmol, 1.0 equiv) or its THF solution (THF was added to adjust the concentration) over 10−15 min while controlling the temperature between 15−25 °C. The resulting solution was stirred at 15−25 °C for 2−12 h, after which HPLC analysis (aliquot into MeOH) showed >95% conversion of bromide. For low concentrations (≤1.1 M for aryl magnesium chloride, ≤0.75 M for aryl magnesium bromide), a reversed addition (addition of *i*PrMgCl/ *i*PrMgBr to a THF solution of trifluoromethyl-substituted bromide) can be applied and proved to be the same outcome. A ∼10 mL sample was withdrawn during or after the completeness of magnesium−bromide exchange and subjected to adiabatic calorimetry study using an ARSST.

Data Collection of Adiabatic Calorimetry. Experimental data were collected using ARSST manufactured by Fauske and Associates.[8] ARSST is a quasi-adiabatic instrument that works on basis of heat loss compensation principle. The basic component of the ARSST includes a spherical 10-mL glass test cell, its surrounding "bottom heater" jacket and insulation, thermocouple, pressure transducer, and a 350-mL containment vessel that serves as both pressure simulator and safety vessel. Tests were performed in the open test cell in closed containment. Nitrogen pressure in the containment vessel is used to suppress the boiling point of the sample. The sample temperature is measured by a thermocouple inside the test cell. A magnetic stir bar is placed inside the test cell and driven by an external magnetic stirrer. A key feature of the apparatus is its low effective heat capacity relative to that of the sample (low φ factor). Thus, the heat released by chemical reaction goes to heat up the sample with negligible energy absorbed by the test cell itself. A fill tube is used to add the mixture to the purged test cell. ARSST containment including the reaction cell was purged many times with nitrogen before introducing the reaction mixture to the system by syringe through the fill tube. All ARSST data were collected with the use of 2 °C/min temperature ramp polynomial. All ARSST data points in the plots were smoothed over five data points. In all experiments 10 mL of the reaction mixture was used.

Supporting Information Available

Adiabatic calorimetry data of all the experiments including temperature−time profile, temperature rise rate−temperature profile, pressure−time profile, and pressure rise rate−temperature profile as well as fluorine analysis of the decomposition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For more information, see: Fauske, H. K. *Process Saf. Prog.* **2006**, *25*, 120.