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AN INVESTIGATION OF FRIEDEL-CRAFTS ALKYLATION REACTIONS IN SUPER- AND SUBCRITICAL CARBON DIOXIDE AND UNDER SOLVENTLESS REACTION CONDITIONS

by

Kan Nie

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Kan Nie

AN INVESTIGATION OF FRIEDEL-CRAFTS ALKYLATION REACTIONS IN SUPER- AND SUBCRITICAL CARBON DIOXIDE AND UNDER SOLVENTLESS REACTION CONDITIONS

Kan Nie, M.A.

Western Michigan University, 2001

This study investigates the Friedel-Crafts alkylation reaction of triphenylmethanol with methoxybenzene (anisole) in supercritical and subcritical carbon dioxide, and under solventless reaction conditions. The reaction was initiated using trifluoroacetic acid to produce triphenylmethylcarbocation as the reaction intermediate. Isolated product yields of the Friedel-Crafts product, p-methoxytetraphenylmethane, are reported. The possibility of using the above reaction as an alternative synthesis in an undergraduate organic laboratory to teach some of the tenets of green chemistry is also presented. Additionally, we have investigated the use of benzhydrol, 9-hydroxyxanthene and 9-phenylxanthen-9-ol as potential carbocation sources for supercritical carbon dioxide synthesis and we report those preliminary results.

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INTRODUCTION

Properties of Supercritical Fluids

The ability of supercritical fluids (SCFs) to act as solvents has been known for well over a century[1] but the most significant developments in the application of this technology have taken place just in the last few decades. Among their very most recent applications, SCFs have been employed as media for chemical reactions. As a reaction medium, the SCF may either participate directly in the reaction or act as a solvent for the various chemical species. The physical properties of SCFs are highly dependent on pressure and temperature which makes it possible to fine-tune the chemical reaction environment. These characteristics are unique to SCFs and provide the potential to tune the chemical reaction environment in order to optimize reaction rate and selectivity.

The definition of supercritical fluid as described by the IUPAC[2] refers to a SCF as the defined state of a compound, mixture or element above its critical pressure (P_c) and critical temperature (T_c) but below the pressure required to condense it into a solid (Figure 1).[3] As defined by T_c and P_c, the critical point marks the end of the liquid-vapor coexistence curve in the phase diagram for a pure substance, as shown in Figure 2.[4] A supercritical region originating from the critical point can be identified in this phase diagram. Generally, only a single homogeneous phase can exist in the supercritical region, irrespective of the temperature and pressure. However, solidification may also occur at very high pressure. Changes in phase from liquid to vapor are accompanied by unexpectedly sudden changes in physical properties but, in the supercritical region, properties may be varied continuously by manipulating the temperature and pressure. It is also possible to construct the path shown in Figure 2, where the progression from a liquid state (A) to a gas state (B), and vice versa, proceeds without any visual signs of boiling or condensation.

The properties of SCFs vary over a wide range depending on the temperature and pressure but are intermediate to those of gases and liquids. Some selected physical properties of SCFs are shown in Table 1 together with typical values for gases and liquids. The properties of SCFs are sensitive to small changes in temperature and pressure in the vicinity of the critical point.

Table 1

Comparison of the Physical Properties of Gases, Liquids and SCFs[5]

Property	Gas	SCF	Liquid
Density (g/mL)	10^{-3}	0.3	1
Viscosity (Pa s)	10^{-5}	10^{-4}	10^{-3}
Diffusivity (cm^2/s)	0.1	10^{-3}	5×10^{-6}

Supercritical fluids have a number of obvious advantages over conventional liquids. The adjustable solvent strength and favorable transport properties differentiate SCFs from liquid solvents. Most SCFs are low-molecular-weight gases which have relatively low critical temperatures. Therefore operations may be carried out at moderate temperatures which is desirable in the recovery of thermally labile materials. Perhaps the most importment advantage offered by SCFs is that components are left virtually free of residual supercritical solvent after the release of pressure.

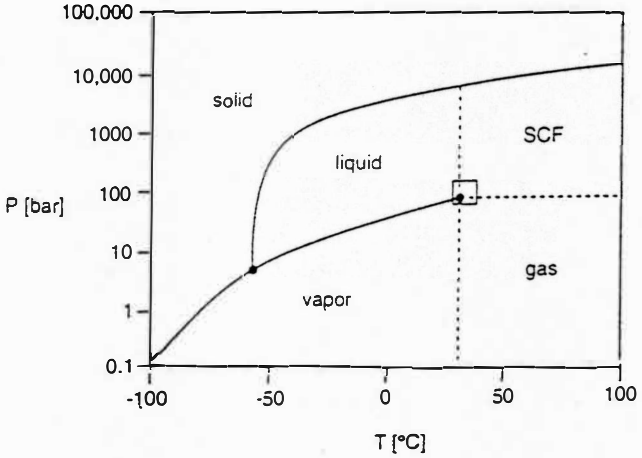


Figure 1. The Phase Diagram of CO_2.[3]

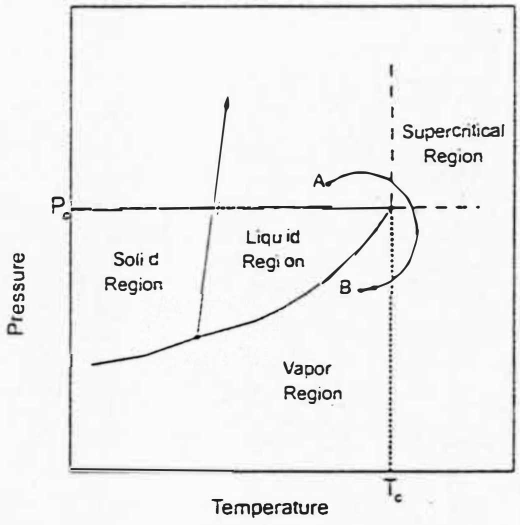


Figure 2. Phase Diagram for a Pure Substance.[4]

The majority of studies about SCFs has focused on four fluids: CO_2, ethane, ethene and water. The first three fluids have critical temperatures below 35°C. By far carbon dioxide is the most widely used SCF and has several advantages over the hydrocarbons in that it is nontoxic, nonflammable and readily available in high purity. Carbon dioxide is a moderately good solvent for many low-to-medium molecular weight organics and also exhibits low miscibility with water. The solubilities reported in the literature for nonpolar solids and liquids in CO_2 range from 0.1 to 10 mol%. Marginally higher solubilities can be obtained in ethane and ethene.

Other commonly used SCFs and their critical properties is given in Table 2.[6] It is evident from this table that SCFs generally require the use of pressure in excess of at least 40 bar. It is interesting that linear hydrocarbons generally have a critical pressure below 50 bar and a critical temperature that increases with molecular weight. Additionally, substances capable of hydrogen bonding require relatively high critical temperatures and pressures.

In some applications, the pressure required for a SCF process may result in very high capital investment for process equipment. However, it is possible to increase the solvent power of a primary SCF with the addition of small amounts (typically ~1-5 mol %) of cosolvents, such as methanol or acetone. The significance of this addition is that lower operating pressures (and temperatures) are made possible.

Supercritical fluids are now widely used for supercritical fluid extraction, supercritical fluid chromatography, and in food and natural products processing.[7] Other applications[8] of SCFs that are becoming more popular are in the fields of materials processing,[9] pharmaceuticals,[10] biotechnology,[11] environmental remdiation,[12] pollution prevention[12] and reaction engineering.[8, 13]

Table 2

Critical Data of Supercritical Fluids[6]

Solvent	Critical Temperature (°C)	Critical Pressure (bar)
CO_2	31.0	73.8
N_2O	36.4	72.5
Ethane	32.3	48.8
Ethene	9.2	50.5
Propane	96.7	42.5
Propene	91.7	46.0
Ammonia	132.4	113.5
Methanol	239.5	81.0
Water	374.0	220.6
CHF_3	26.2	48.5
$CClF_3$	28.9	38.7
SF_6	45.5	37.7

Chemical Reactions Under Supercritical Conditions

Carbocation Reactivity in Supercritical CO_2

In recent investigations of electron transfer reactivity of excited-state carbocations in supercritical carbon dioxide (SC CO_2), it has been demonstrated that, under mildly acidic conditions, [14] stabilized carbocations, e.g., triphenylmethyl cation, xanthenium cation and 9-phenylxanthenium cation, could be generated from their corresponding alcohols in CO_2. for example, see figure 3 for the generation of 9-phenyxanthenium cation.

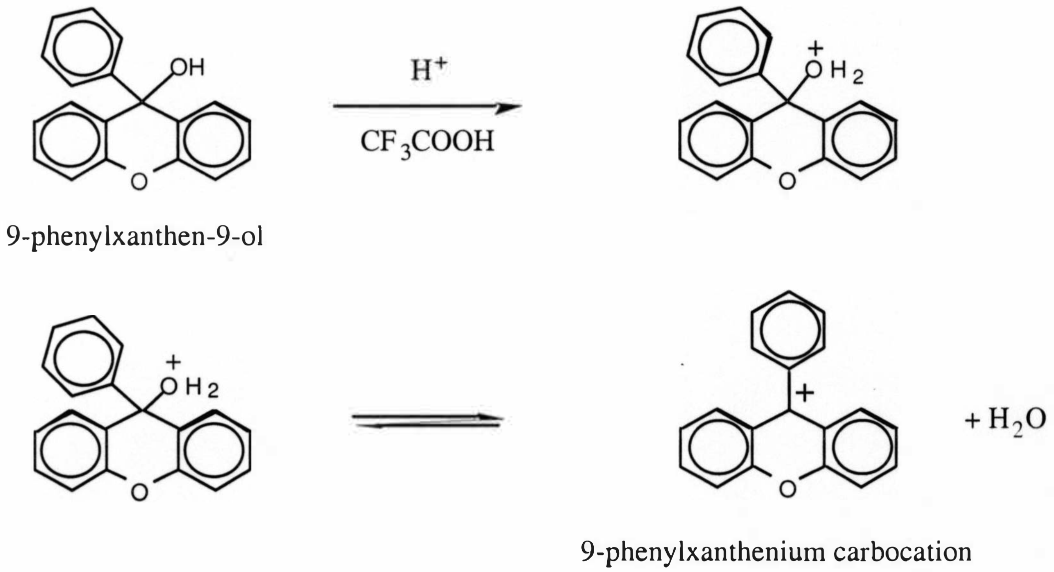


Figure 3. Generation of 9-Phenylxanthenium Carbocation.

From *In situ* UV-visible spectroscopy it had previously been demonstrated[14] that under these conditions the carbocations were stable for days. This stability provided a way to generate photo-excited carbocations and measure their corresponding rates of decay using fluorescence spectroscopy. The pressure, and corresponding solvent density, dependence of the absolute reactivity of electron transfer between excited-state 9-phenylxanthenium cation and toluene, which act as the electron donor [15,16] had been specifically investigated in the master's thesis work of Hongshu Jin.[14] During these experiments it had been noticed that the ground state of the carbocation was slowly being consumed (Figure 4) in the presence of toluene. This observation suggested the possibility that an aromatic (Friedel-Crafts) alkylation reaction was possibly occurring under these SC reaction conditions.

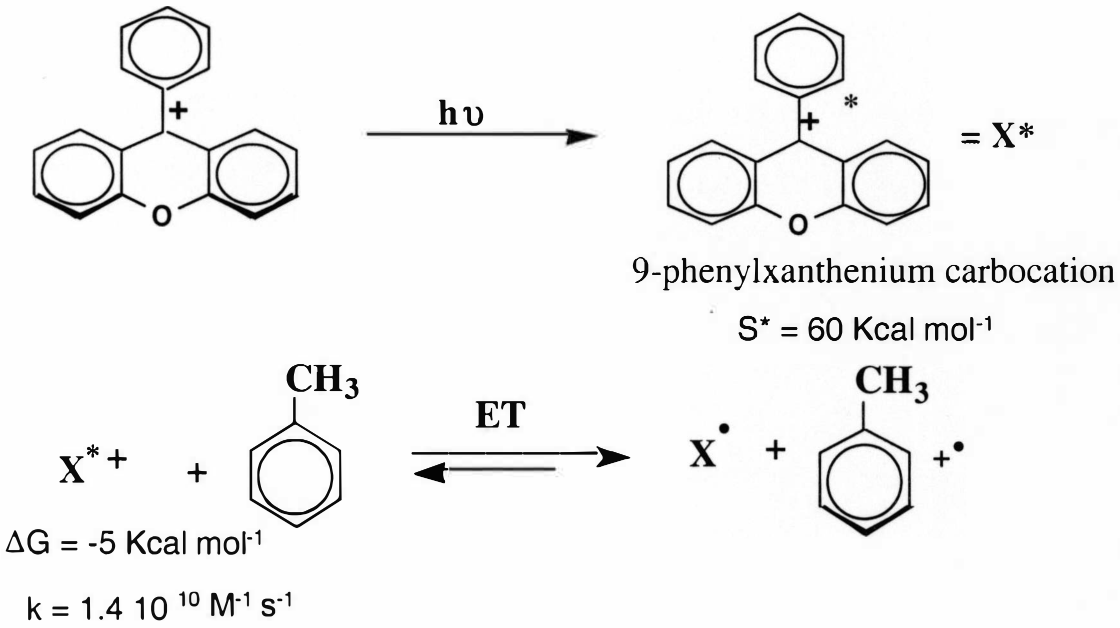


Figure 4. Scheme Describing the Electron Transfer Reaction Between Excited State 9-Phenylxanthenium Carbocation and Toluene.[43]

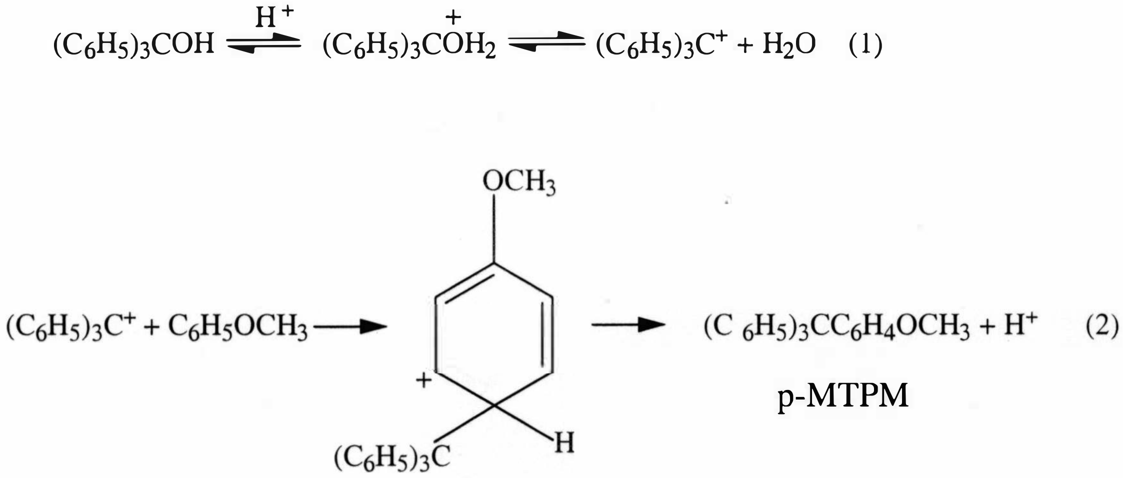
Friedel-Crafts Alkylation Reaction

Many chemical syntheses involve Friedel-Crafts or Friedel-Crafts-type alkylation reactions, both on laboratory and industrials scales. Friedel-Crafts chemistry is therefore of major importance in research.

At present time, there is significant interest in the development of green chemistry [17] and one of the maturing area of green chemistry is the use of more environmentally friendly reaction media, such as SC fluids, [19] as alternatives to traditional organic solvents. In this regard, we decided to pursue the practicality of performing Friedel-Crafts (FC) reactions under homogeneous SC reaction conditions with CO_2 as reaction media. In conventional solvents, FC reactions are usually performed using strong Bronsted acids (H_2SO_4 and HF) or Lewis acids ($AlCl_3$ and BF_3). These reactions generally require more than one stoichiometric equivalent of FC catalyst and produce large quantities of waste that are often difficult and costly to separate from the desired product. As a result, traditional FC reactions using strong Bronsted acids or Lewis acids are far from being atom efficient, nor can they be considered environmentally friendly. [20] In contrast, the previously mentioned SC CO_2 reaction condition[14-16] seemed very promising, in that we were using relatively small quantities of trifluoroacetic acid (TFA) as our protonation source, i.e., FC catalyst, and depressurization methodologies could be employed to recycle acid used and the majority of the CO_2 solvent.

The preparation of *p*-methoxytetraphenylmethane (p-MTPM), see Figure 5, was chosen for the initial FC synthesis[21] as an example of FC aromatic alkylation. This reaction was chosen for the following reasons: 1) Our group had previously determined that a reaction mixture of triphenylmethanol and TFA (1.0×10^{-3} M and 2.6×10^{-2} M, respectively) are soluble in SC CO_2 at moderate pressures (ca. 100-150 bar) and produced triphenylmethyl cation from previous spectroscopic measurements. 2) Methoxybenzene is extremely reactive toward electrophilic substitution, and 3) p-MTPM is easily identified as an isolated product, m.p. = 201-202°C, and the product yields could be directly compared to a conventional (glacial acetic acid / sulfuric acid solvent) preparation of p-MTPM. [22]

Scheme 1



$$(C_6H_5)_3COH \overset{H^+}{\rightleftharpoons} (C_6H_5)_3C\overset{+}{O}H_2 \rightleftharpoons (C_6H_5)_3C^+ + H_2O \quad (1)$$

Figure 5. The Mechanism of p-MTPM Production.

Figure 5 presents the mechanism of p-MTPM production. The oxonium intermediate undergoes loss of water to produce triphenylmethylcarbocation following initial protonation of triphenylmethanol. In a second step, methoxybenzene undergoes electrophilic substitution by forming an intermediate sigma complex, followed by p-MTPM production with a proton being released to the medium.

Background information regarding FC synthesis that use homogeneous SC fluids as the reaction medium is limited. For the specific case of SC CO_2, this is undoubtedly due to extremely low solubility of conventional FC catalysts in CO_2. However, FC alkylation reactions have been reported using high-temperature (near-critical) water as a homogeneous reaction medium.[23, 24] Eckert and coworkers demonstrated phenol and p-cresol could be alkylated with *tert*-butyl alcohol and 2-propanol in water at $275^{\circ}C$ in the cresol could be alkylated with *tert*-butyl alcohol and 2-propanol in water at 275°C in the absence of added acid catalyst. Therefore, water acted as both the solvent and catalyst under the near-critical conditions used in those investigations. There is significantly more background information regarding the use of SC fluids for heterogeneous catalysis,[25] and specifically the use of solid acid catalysts for FC reactions. [26, 27] The examples of solid acid catalysts include: zeolites, mixed metal oxides, functionalized polymers and supported reagents. Solid acid catalyst have been used widely in the petroleum industry for vapor phase continuous process operations. In contrast to vapor phase operation, condensed phase operation is very problematic due to catalyst deactivation by coke formation. Currently, SC fluid operation has been used in order to slow catalyst deactivation by taking advantage of the high diffusivity of SC fluids to more quickly remove products and by-product from the catalyst. There are several reports in the literature of SC operations using solid acid catalyst for FC alkylations. Most of these reports are about alkylations of hydrocarbons that have relatively low critical temperature (Tc) and critical pressure (Pc). Therefore, SC operation simply refers to running the chemical reaction above the critical property of the reaction mixture. For example, consider the alkylation reaction of isobutane and isobutene using a zeolite catalyst and isobutane as the solvent, the reaction was run at 50-140°C and 3.5-5.0 Mpa. [25] There are some other reports, however, that have used SC CO_2 as either a diluent or as the solvent. As an example, Hitzler et al. [27] have reported the alkylation of mesitylene and propan-2-ol using SC CO_2 as solvent and polysiloxane (BELOXAN) supported solid acid catalyst. Other examples can be found in a review of heterogeneous catalysis in SC fluids. [25] The following reports the details of the p-MTPM synthesis and yield of p-

MTPM produced under both super and subcritical CO_2 conditions and under solventless reaction conditions. Also presented are attempts to react three other carbocations of varying structure and stability with anisole and benzene in supercritical CO_2. In addition, the possibility of using the above reaction as an alternative synthesis in an undergraduate organic laboratory to teach some of the tenets of green chemistry are presented.

Green Chemistry and Applications

The Definition of Green Chemistry

The definition of Green Chemistry, as described by Anastas and Warner,[18] is "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products." Green chemistry[28, 29, 30] is a special type of pollution prevention. While there are other methods of achieving pollution prevention that are very useful and necessary options, green chemistry is an approach that provides a fundamental methodology for changing the intrinsic nature of a chemical process so that it is inherently of less risk to human health and the environment.

The listing of the "Twelve Principles of Green Chemistry" could be viewed as a reflection of the science that has been done within this new field in the recent years, as well as a direction that has been set by some of the pioneering scientists who have laid the groundwork for the future (Table 4). [18]

Table 4

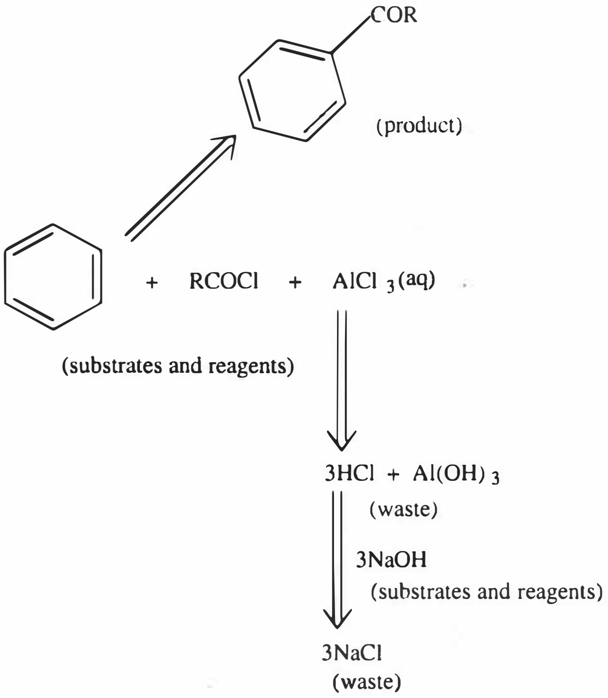
Twelve Principles of Green Chemistry[18]

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Important Generic Area of Chemistry[31]

To help illustrate the many challenges ahead and the opportunities for new green chemistry, one very broadly based generic area of chemistry-acid catalysis can be at least superficially examined in terms of its scope, the environmental unacceptability and poor atom economics of typical processes, and the goals and possible approaches of green chemistry.

Friedel-Crafts acylation (including benzoylations and sulfonylations) are real and alarming examples of very broadly used acid-catalysed reactions which are based on 100 years old chemistry and are extremely wasteful. The reaction of an acid chloride with an aromatic substrate requires a greater than stoichiometric quantity of aluminium chloride which acts as the "catalyst" (>2 mole equivalents in sulfonylations). Every molecule of the ketone product produces a complex with one molecule of the catalyst, effectively removing it from the reaction. By using a water quench, the organic product is released with the resulting emission of about 3 equivalents of HCl, which need to be scrubbed from the off gases and leads to the production of 3 equivalents of salt waste. As soon as the organic product has been recovered, aluminous water remains, which must also be disposed. The overall process generates more waste than product (Figure 5).



Substrates and Reagents	1000 arbitrary weight units
Products	120 arbitrary weight units
Waste	880 arbitrary weight units

(based on R = Me and weight units calculated from relative molar masses)

Figure 6. Friedel-Crafts Acylation Showing a Typical Starting Materials/Products/Waste Balance [20]

Many other industrial processes are catalysed by $AlCl_3$. These include alkylations and the production of resin via cationic polymerization. While these reactions do not require the use of stoichiometric quantities of the Lewis acid, all such processes show the same atom utilization and none of the catalyst is recovered (Table 5).

Table 5

Atom Utilization in a Typical $AlCl_3$-Catalysed Friedel-Crafts Acylation [20]

Element	Fate	Atom utilization
Carbon	Products and by-products	Up to 100%
Hydrogen	Products, by-products and waste (from quench)	<<100%
Aluminium	Aluminous water/aluminium salts	0%
Chlorine	Waste water (from quench) and salt (from HCl scrubbing)	0%
Oxygen	Waste water	Down to 0%

The green chemistry goal for such reactions should be to remove all elements from the accounts other than those involved in the organic chemistry and, of course, to push the organic chemistry towards 100% selectivity to the desired product.

A number of new, more environmentally friendly acids for conventional liquid phase, specially solid acids (which are generally easier and less energy and resource consuming to recover than soluble acids), are beginning to find their way into industrial usage. These include zeolites,[32] clays and other mixed metal oxides, inorganic-organic composite materials, supported reagents[33, 34] and functionalised polymers as well as lanthanide triflates.[35] Other interesting "green" solutions to the problem include the use of ionic liquids.[36]

EXPERIMENTAL

Materials

Triphenylmethanol (97%), methoxybenzene (99%), benzene (99+%), trifluoroacetic acid (99%), benzhydrol (95%), 9-hydroxyxanthene (98%), 9-phenylxanthen-9-ol (98%) and chloroform-d (99.8 atom % D) were purchased from Aldrich and used as received, as was the dichloromethane, Acros Organics (GC grade). Eastman Kodak Co. Chromagram Sheet 13181 (100-micron silica gel) thin layer chromatography plates were used for analytical chromatography and Fisher 28-200 mesh silica gel was used for column chromatography. The GC-MS system used was a Hewlett Packard HP 6890 series GC (HP-5MS column) with a Hewlett Packard 5973 mass selective detector. ^{1}H NMR experiments were performed using a JEOL Eclipse (Peabody, MA) 400MHz NMR spectrometer.

Authentic samples of p-MTPM were prepared using a conventional synthesis as described by Wilcox and Wilcox.[22] Briefly, in a 250 mL round bottom flask, 3.0 g (0.012 mole) of triphenylmethanol was added to 9.0 mL (0.083 mole) of anisole, followed by 85 mL glacial acetic acid and 8.5 mL concentrated sulfuric acid. The solution was stirred magnetically and refluxed for 1 hour. After cooling, the solution was poured into 100 mL of water and the white precipitate was collected on a Buchner funnel and recrystallized from 1:1 (v:v) toluene:2-propanol which gave 35% yield p-MTPM, m.p. = 198-200°C [22]. ^{1}H NMR ($CDCl_3$ was used as solvent, chemical shifts are in ppm relative to TMS as the internal standard, δ 7.25-7.16 (15H, m); δ 7.10 (2H, d, J= 9.16 Hz); δ 6.77 (2H, d, J= 9.16 Hz); δ 3.78 (3H, s). The ^{1}H NMR spectrum (Figure 11) identifies the products as p-MTPM as indicated by the observed chemical shifts and signal integration. Note the characteristic chemical shift of the methoxy methyl protons at 3.78 ppm. Para substitution of anisole is also demonstrated by the distinctive AB splitting pattern of the doublets at 7.10 and 6.77 ppm having identical couping constants, J= 9.16 Hz.

Equipment

The apparatus used to deliver CO_2 to either the high pressure reactor or the high pressure optical cell, *vide infra*, contained the following components: a CO_2 gas cylinder, Air Products (SFC grade), fitted with a diptube; and a model 260D Isco high pressure syringe pump, thermostatted with a water jacket and a Fisher Scientific ISOTEMP 1006s heater/chiller re-circulation bath. Connections to the reactor or optical cell were made with HIP 1/16" stainless steel high pressure tubing and high pressure (HIP) line valves fitted with Teflon o-rings.

The high pressure reactor apparatus (Figure 6) is described elsewhere.[21] Briefly, it was constructed using a custom built cylindrical stainless steel reaction vessel having ca. 79 mL capacity. The vessel was fitted with inlet and exit valves, a Noshok 5000 psi pressure gauge as well as a HIP rupture disk. When in operation, the reactor was magnetically stirred using stirring bar and heated using Omega (Omegalux) heating tape

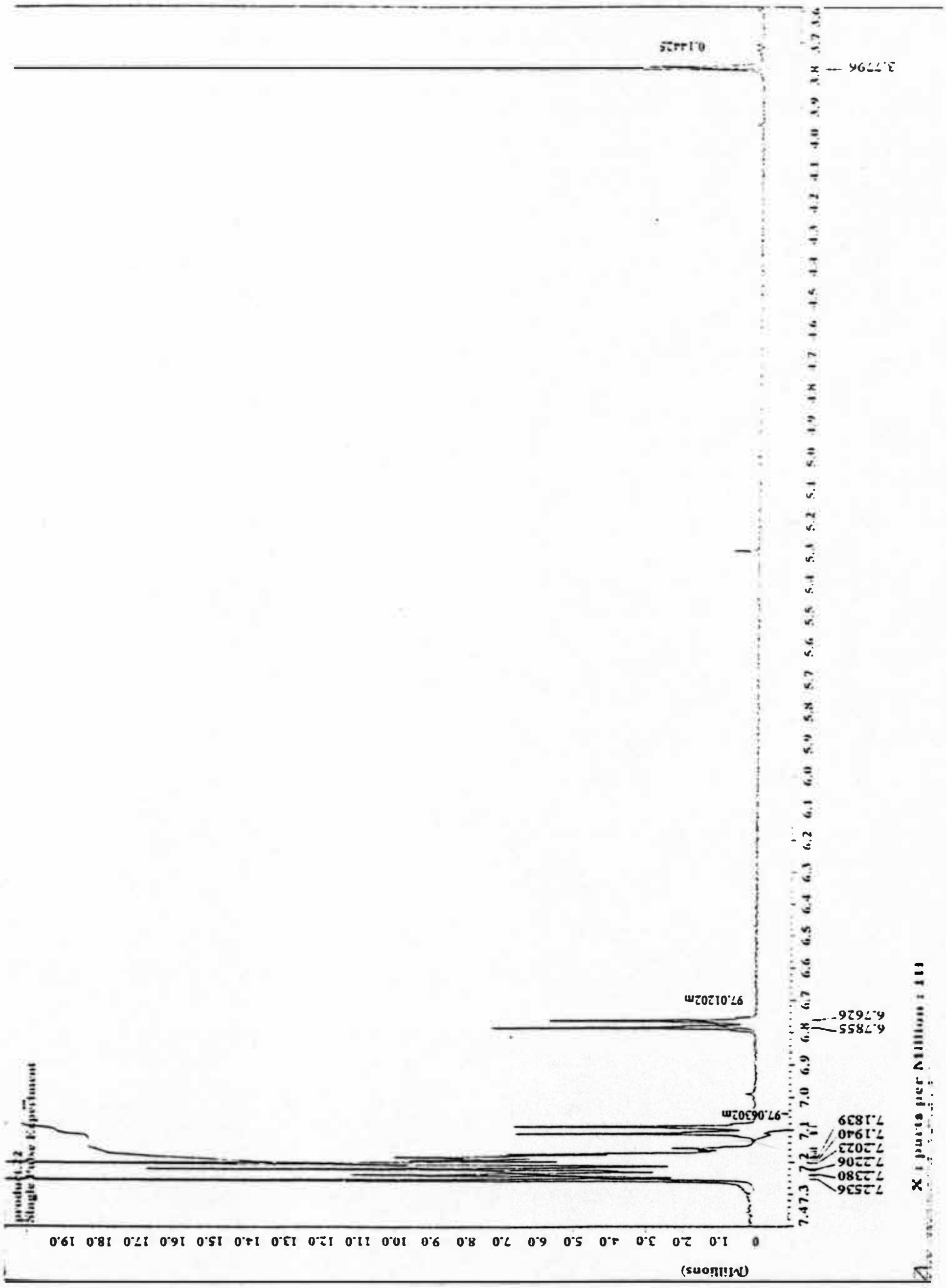


Figure 7. NMR Spectrum of p-MTPM.

that was regulated using a variable voltage regulator. An Omega model HHII digital thermometer and a type K thermocouple were using to monitor the external temperature of the reaction vessel.

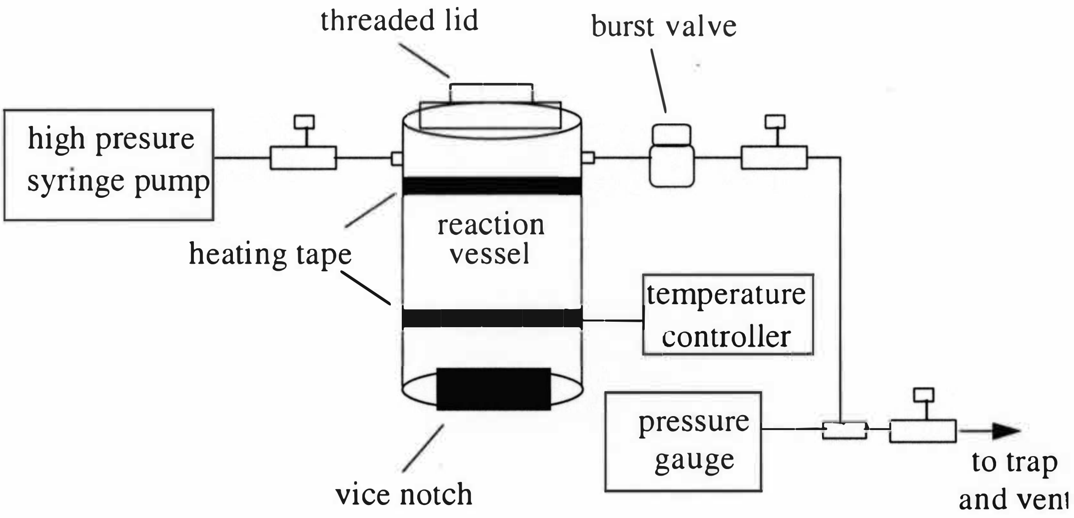


Figure 8. High Pressure Reactor Used for the p-MTPM Synthesis.

The high pressure optical cell (Figure 7) was constructed of stainless steel, had ca. 3 mL capacity (1.7cm optical path length) and was fitted with Suprasil quartz windows having mechanical seals with lead packing. The design, construction and operational use of our optical cells have been described elsewhere.[37] Briefly, an Omega Model CN-6070A temperature controller equipped with a cartridge heater and a platinum resistance thermometer was used to control temperature and a model 901A Heise pressure gauge, Dresser Industries was used to monitor pressure.

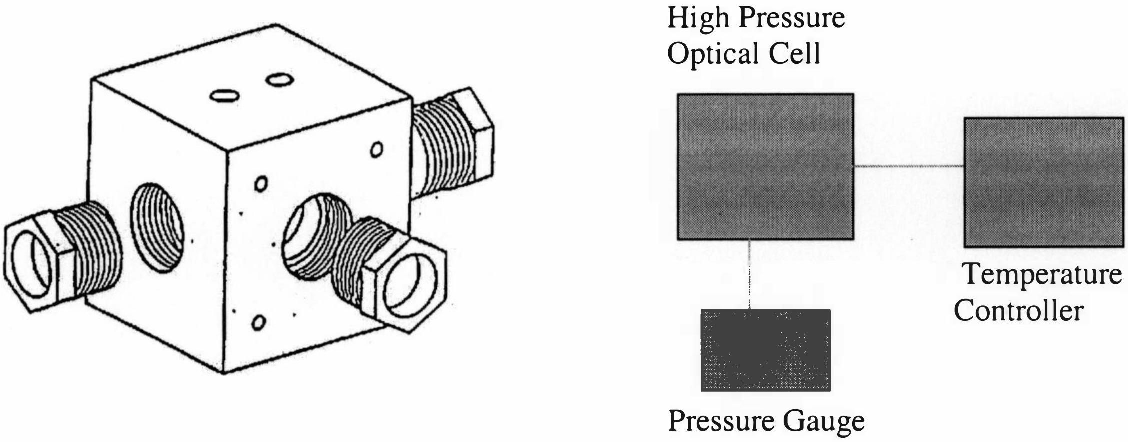


Figure 9. The Optical Cell Used to Observe Phase Behavior.

Procedure: p-MTPM Synthesis

The standard procedure for the experiments that used CO_2 involved placing known amounts of triphenylmethanol (20.54 mg; 1.0×10^{-3} M), anisole (60.00 mg; 7.0×10^{-3} M) and TFA (0.158 mL; 2.6×10^{-2} M) into the reaction vessel and charging the vessel with pure CO_2 from the Isco pump to a pressure that upon heating would generate a desired reaction pressure. Typically, the reactions were maintained at temperature (±2°C) for 16-18 hours (see Table 6). Following cooling to room temperature the reactor was slowly depressurized into a flask containing CH_2Cl_2. The reaction products from the depressurized vessel were also dissolved in CH_2Cl_2 and the combined volumes reduced for chromatography. It should be noted that the mass of material recovered from the reactor indicated no loss of material during depressurization and transfer. p-MTPM was isolated using silica gel column chromatography with CH_2Cl_2 as the eluent.

Table 6

Isolated Yields of p-MTPM Using Super- and Subcritical CO_2

Isolated Yields and Reaction Conditions				
Temp (^oC)	*Pressure (bar)*	**Density (g/cm^3)*	*% Yield*	*Reaction Time*
115	229.5	0.483	3.25	17 hours
70	346.7	0.824	3.62	16 hours
23	208.8	0.929	N/A	17 hours
87	208.8	0.571	3.98	18 hours
91	139.9	0.327	3.62	17 hours
95	84.7	0.154	37.5	16 hours
95	81.3	0.146	36.2	16 hours
95	42.4	0.068	83.2	16 hours

* density of pure carbon dioxide was calculated according to *International Thermodynamic Tables of the Fluid State: Carbon Dioxide.*[38] However, it should be noticed that when certain amount of chemicals mixed with supercritical carbon dioxide, the density of the whole system would be changed, the densities listed here only reflect the *pure* carbon dioxide densities.

TLC, using petroleum ether (30-60) as the developing solvent, was used to analyze fractions. Fractions contained only p-MTPM, as compared to authentic samples ($R_f = 0.3$) were combined and the solvent removed *in vacuo*. Isolated product yields for the experiments performed using super- and subcritical CO_2, they are presented in Table

6. The conditions and results of the reaction performed under conditions other than CO_2 are presented in Table 7.

Table 7

Isolated Yields of p-MTPM Under Solventless Reaction Conditions

Isolated Yields and Reaction Conditions					
Atmosphere	*Temp. (^oC)*	*Pressure (bar)*	*Density (g/cm^3)*	*% Yield*	*Reaction Time (hrs)*
[a] N_2	94	1.0	N/A	83.2	17
[a] N_2	95	1.0	N/A	86.8	16
[b] Neat/CH_3CO_2H	118	1.0	1.049	3.65	1
[b] Neat/CF_3CO_2H	72.4	1.0	1.480	83.2	1

a) In high pressure reactor.
b) Refluxed in 25 mL round bottom flask (open to air).

Procedure: Other Cations

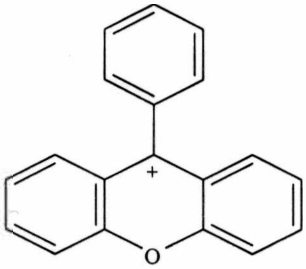
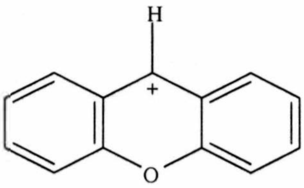
The procedure used to generate cations from 9-hydroxyxanthene, benzhydrol and 9-phenylxanthen-9-ol (Table 8) was identical to those described for the p-MTPM synthesis. However, work-up and analysis was accomplished by dissolving the crude reaction mixture (the combined volumes reduced) in a few milliliters of CH_2Cl_2 and performing GC-MS analysis.

Procedure: The Green Chemistry Experiment

The procedure for the green chemistry experiments are described in the section of green chemistry Results and Discussion.

Table 8

Carbocations Investigated

	Carbocations		**Product**
1.	Ph_3C^+	Triphenylmethylcarbocation	
2.	Ph_2HC^+	Benzhydryl cation	ether product <10% FC product
3.		9-Phenylxanthenium cation	No product
4.		Xanthenium cation	ether product <10% FC product

RESULTS AND DISCUSSION

Triphenylmethylcarbocation

Table 6 presents the isolated percent yields of p-MTPM under a series of variety reaction conditions. For the reactions performed using CO_2 as the reaction medium the fluid density of CO_2 is also given. These fluid densities are of pure CO_2, and were calculated using the method of Angus.[38] Of course, the phase behavior of pure CO_2 does not accurately describe the reaction mixture. Nevertheless, the calculated CO_2 densities are qualitatively helpful. Spectroscopic and visual observation of the phase behavior of the reaction mixture was performed for two specific reaction conditions, one high density and one low density, *vide infra*.

The initial experiment was conducted at 115°C. This temperature was chosen to resemble the thermal conditions of the conventional synthesis performed in acetic acid solution, the b.p. of acetic acid is 118°C. The reaction pressure was 229.5 bar, which corresponds to a solvent density (pure CO_2 density) of 0.483 g/cm^3. The critical density of CO_2 is 0.468 g/cm^3. [39] Therefore, the reaction mixture density should be, at the very least, near critical. The isolated percent yield of the product for this reaction was 3.25% (see Table 6), which was far below the yield of ~35% obtained in the conventional synthesis. We realized that at this near critical density it was possible that the reactants were not all in a single phase. In an attempt to improve the yield, we increased the fluid density to ca. 0.824 g/cm^3 by lowering the reaction temperature to 70°C and lifting pressure at 346.7 bar. At a comparable elevated density, both visual inspection and spectroscopic detection (*vide supra*) indicated a single phase for the reaction mixture. Interestingly, at this liquid-like density, the yield of product remained at 3.62%. To determine whether elevated temperature was necessary to produce p-MTPM, we performed a reaction at room temperature (23°C) and at 208.8 bar CO_2 pressure. Followed by our standard work-up procedure, no isolated product was obtained. This is estimated to be less than 1%. This experiment also indicated that, prior to charging the vessel with CO_2, there was no significant production of p-MTPM in the reaction vessel. To confirm that significant quantities of p-MTMP were not being produced simply upon mixing of the reactants at room temperature, a test tube experiment was performed in which the reactants were combined and stay in the test tube for 1 hour. This experiment also resulted in no isolated p-MTPM. Therefore, albeit in very modest yields, we were confident that the FC alkylation reaction described above was occurring under homogeneous SC CO_2 reaction conditions during a certain period of time.

The next series of experiments were designed to determine whether the yield of the FC reaction could be significantly influenced by varying CO_2 fluid density or not. It is well known [40] that attractive forces between solutes and SC fluids may result in "supercritical solvent clustering" at near critical conditions. That is, a higher local density of solvent than the bulk density of solvent is found around the solute. In addition, attractive forces between a solute and a co-solute, or co-reactant may result in an increase in the local composition of the co-solute about the solute. This has been referred to as co-solute "clustering", or enhanced local composition. [40] These phenomena tend to be most prevalent at near critical fluid densities. In fact, both solvent density augmentation and local composition enhancement have been shown to be greatest at densities below the critical density of mixtures.[40, 41]

Keeping in mind the possibility of local microstructure influencing the FC reaction, a series of experiments were performed at approximately the same temperature range at 87-95°C and reaction pressures ranging from 208.8 to 81.3 bar. The corresponding CO_2 density for the reactions ranged from SC density (0.571 g/cm^3) to near-critical, or sub-critical density (0.327 g/cm^3), and to well below the critical density (0.154 and 0.146 g/cm^3). The super and near-critical experiments resulted in 3.98 and 3.62% yields, respectively. Therefore, considering this and the initial data presented above, it would appear that there was no significant influence of local composition influence on this FC reaction. That is, the yields from the experiments performed at higher, liquid like densities were essentially the same as those obtained from the experiments performed in the near-critical regime. It is in that latter, highly compressible regime where local composition effects are usually more prevalent.[40-42] At the lower densities (0.154, 0.146 and 0.068 g/cm^3) the percent yield dramatically increased to 37.5, 36.2 and 83.2%, respectively. However, the CO_2 density was calculated to be far below the critical density of CO_2 at those reaction conditions. As a result, the reaction would certainly be occurring under subcritical conditions. That was verified visually by observing a liquid phase (Figure 8) in a high pressure optical cell. Therefore, the reaction was most likely occurring in essentially neat, CO_2 rich, liquid reactants.

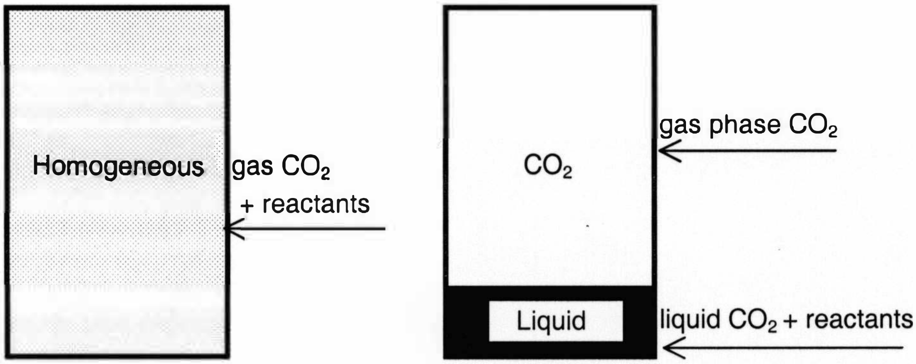


Figure 10. Difference Between Supercritical CO_2 and Split-phase CO_2.

To verify that the dramatic yield increase observed at the lowest CO_2 densities was due to subcritical reaction conditions, experiments were performed using the standard reaction concentrations described above, however, replacing CO_2 with 1 atmosphere of N_2 at 95°C. The results were approximately 83-87% yield p-MTMP, see Table 7. Finally, two experiments (one using TFA and one using acetic acid) were performed, using same amounts of reactants as in the high-pressure reaction, however, this time the reactions were performed in a small round-bottom flask, equipped with a condenser, and the reactants were refluxed for 1 hour. In both the TFA and the acetic acid experiments, the reaction mixtures liquefied upon heating. Thus, the reactions were performed in essentially a neat liquid mixture. The results were 83.2% yield in TFA and only 3.65% yield in acetic acid.

The above results demonstrate that it is not always advantageous to perform experiments under homogeneous supercritical reaction conditions. For certain applications, it may be far more beneficial to perform reactions under subcritical, or solventless reaction conditions.

Other Carbocations

The next series of experiments attempted to improve the yield of an anisole FC product in supercritical CO_2 by changing the reactivity of the carbocation. The cations generated other than triphenylmethylcation were benzhydryl cation, 9-phenylxanthenium cation and xanthenium cation, see Table 8. These cations were generated using trifluoroacetic acid and the respective alcohols are benzhydrol, 9-phenylxanthen-9-ol and 9-hydroxyxanthene. The strategy and the initial results are presented below. Believing a significantly increase in the FC product yield could be obtained by using a carbocation less stable than triphenylmethylcarbocation, benzhydrol was first chosen to perform the same type of supercritical CO_2 experiment described above, in this case to generate Ph_2C^+H. However, upon placing the reactants (Ph_2CHOH /anisole /trifluoroacetic acid) together in the reactor it was obvious, from a dramatic color change, that product formation occurred upon mixing. GC-MS analysis indicated that the expected FC product was formed. In an attempt to relieve this "mixing problem" a 10mL beaker was placed in the reactor in order to separate the trifluoroacetic acid from the alcohol until the cell was charged with liquid CO_2. Both Ph_2CHOH and anisole were placed in the beaker and the acid was added to the bottom of the reactor. CO_2 was then added, and the reactor brought to temperature (using the heating procedure described before). After the reaction time was complete, the cell was depressurized and the beaker was found to be upright and empty. Since the alcohol is a solid, this indicated that the alcohol was dissolved by CO_2, and mixing of the alcohol and trifluoroacetic acid occurred in homogeneous CO_2. Again, GC-MS analysis showed that the expected FC product was produced. (It should be noted, however, that we can not rule out the possibility that the reaction did not occur in the supercritical CO_2, phase and that the reaction simply occurred upon depressurization and re-mixing of the reactants in the bottom of the reactor). However, unlike the Ph_3COH experiments, a second major product was formed in addition to the FC product. The second product was the ether (Figure 13) generated from the attack of Ph_2C^+H on the alcohol precursor, followed by loss of a proton, i.e., $Ph_2CHOCHPh_2$. In order to slow the reaction that occurred upon mixing, benzene was substituted for anisole, since benzene is approximately two orders of magnitude less reactive towards electrophilic substitution than anisole. Before performing the high pressure experiments, a test tube experiment was performed in which certain amounts of the reactants (Ph_2CHOH / benzene / trifluoroacetic acid) were placed in a test tube at room temperature for two hours. This experiment resulted in production of the FC product (Ph_3CH), however no precursor addition adduct ($Ph_2CHOCHPh_2$) was found. Even thought this was not a promising result, an experiment was performed using the beaker separation method in SC CO_2 at 92 °C and 300 bar pressure for 17 hours. Interestingly, in addition to the FC product, $Ph_2CHOCHPh_2$ was also produced along with higher molecular weight adducts. At this time the additional adducts are not definitely identified, although they appear to be products formed from free radical addition (sometimes multiple free radical addition products) to the FC product and the initial alcohol adducts.

As a result of these observations, Ph_2C^+H was considered far too reactive for our purpose, therefore during our next series of experiments we chose to test 9-phenylxanthen-9-ol and, in turn, the generation of 9-phenylxanthenium cation. With this cation we did not observe product upon mixing in either a test tube or in the bottom of the high pressure reactor. Experiments were performed using anisole as the co-reactant under supercritical fluid conditions. Interestingly, GC-MS analysis detected neither FC product nor the ether corresponding to attack of 9-phenylxanthenium cation from 9-phenylxanthen-9-ol. Apparently, 9-phenylxanthenium's stability, or its steric crowding of the cationic center prevented a successful, or irreversible attack at the cationic center. In fact, the residue of the experiment retained the cations characteristic yellow color, which was immediately destroyed by the addition of a small quantity methanol, a fairly good qualitative test of the presence of a stable cation.

Next 9-hydroxyxanthene was chosen as the alcohol in order to generate xanthenium cation. This should remove the extra resonance stability and the steric interference of the 9-phenyl substituent of 9-phenylxanthenium cation. In fact, this was the case and again cation and product formation (both FC product and the product formed from attack of the precursor alcohol on xanthenium cation) were observed upon adding the reactants (alcohol/anisole/acid) in a test tube or in the high pressure reactor. Next, a supercritical CO_2 (beaker) experiment was performed and surprisingly, and at this time unexplained, only the corresponding ether product was observed. Experiments were also performed using benzene as the co-reactant. Again the FC product was not observed but only the ether product was detected. It is obvious that, the reactions in supercritical CO_2, or at least using this supercritical CO_2 procedure, result in different chemistry than that observed under neat room temperature conditions, and these interesting results should be fully examined further. In order to do this properly, our reactor should be modified with on line analysis. It is unfortunate that attempts to generate these particular carbocations in homogeneous supercritical CO_2 have not been successful as a practical solvent for FC alkylations.

Interestingly, however, when both the FC and the alcohol / cation adduct were both formed, an increase in the ratio of FC product to the alcohol ether adduct was detected in the supercritical CO_2 experiments. This indicated that under homogeneous supercritical CO_2 conditions the FC pathway was able to compete with the attack of the carbocation by the alcohol precursor. This, at least, demonstrates somewhat different chemistry than that observed in neat liquids.

Green Chemistry Experiment

From the previous results presented in the last entry of Table 7, this experiment has excellent potential for the development of a green chemistry undergraduate laboratory experiment. This experiment would demonstrate to students the relatively new chemical concepts of green chemistry, which are now being implemented in almost all sectors of the chemical industry world wide. The green chemistry concepts that will be demonstrated are designing new synthetic methods which not only result in higher yields of product compared to conventional synthesis, but also reduce quantities of reactant, auxiliary solvents and waste. This experiment will also demonstrate a reduction in the use of corrosive materials, which in turn relates to lower environmental and worker health risks, the ability to recycle materials and in some cases the reduction of energy, time and labor costs.

First, a conventional FC alkylation synthesis of p-MTPM as described in the undergraduate organic laboratory text of Wilcox and Wilcox [22] will be presented. The second edition of the text published in 1995 describes two possible procedures for the p-MTPM experiment. In both cases, experiments are performed using 250 mL reaction vessels, the first an Erlenmeyer flask and the second a round bottom flask. The reactants were identical in quantity and were 3.0 g of Ph_3COH, 9 mL of anisole, 85 mL glacial acetic acid and 8.5 mL sulfuric acid. The first experiment was performed by simply mixing the reactants together and allowing them to sit in a hood for 2-7 days. The work-up consisted of pouring the product mixture into a 100 mL of water and collecting the precipitate using a Büchner funnel, with a wash of a few milliliters of diethylether. Recrystallization from 1:1 (v:v) toluene:2-propanol resulted in 45% of the theoretical yield. The second option was to accelerate the reaction by refluxing the reactant for 1 hour, followed by the same work-up procedure which resulted in a 35% yield of p-MTPM.

The green chemical alternative to the conventional experiment was performed using a 50 mL round bottom and the new quantities of reactants are: 200 mg Ph_3COH, 0.60 mL anisole and 1.60 mL TFA. The reactants were refluxed for 1 hour and then the TFA, containing remaining quantities of anisole and a small quantity of water, was distilled from the reaction vessel by simple distillation. The volume of distillate recovered was 1.60 mL and GC-MS analysis determined that 1.30 mL of the distillate was TFA. Remaining in the round bottom flask was crude, but relatively uncontaminated p-MTPM recovered in approximately 70% yield. Without the additional labor of purifying the distillate, i.e., the FC catalyst (1.30 mL mixture) was reused with a fresh quantity of Ph_3COH and anisole reactants and the experimental procedure was repeated. The second experiment again gave ~70% yield p-MTPM and ~1.60 mL distillate, however this time the distillate contained 1.13 mL TFA. The recycling experiment was repeated for a total of four runs with a consistent ~70% yield p-MTPM and a total reduction of FC catalyst of a little less than 50% (Figure 9, 10).

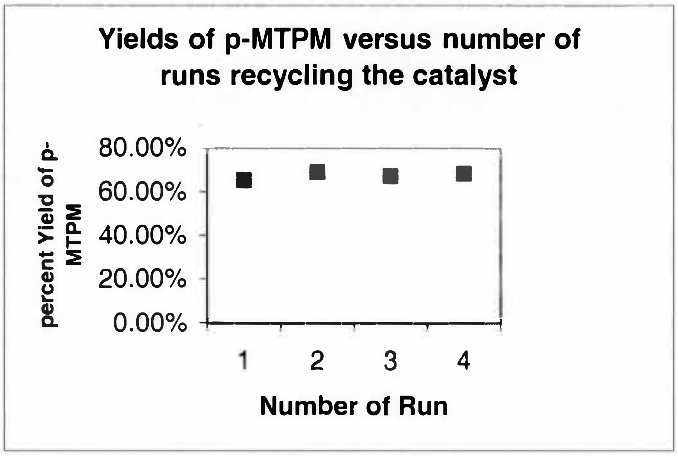


Figure 11. The Yields of p-MTPM Versus Number of Runs Recycling the Catalyst.

The next experiment was to determine how little TFA could be used to reach the similar yields under the experimental conditions described above. The procedure includes placing 200 mg Ph_3COH and 0.60 mL anisole in a 50 ml round bottom flask. In the first trial 0.4 mL of TFA was used, followed by using 0.3 mL, 0.2 mL, 0.1 mL, 0.06 mL, 0.05 mL of TFA. The reactant mixtures were refluxed for 1 hour. The percent yield

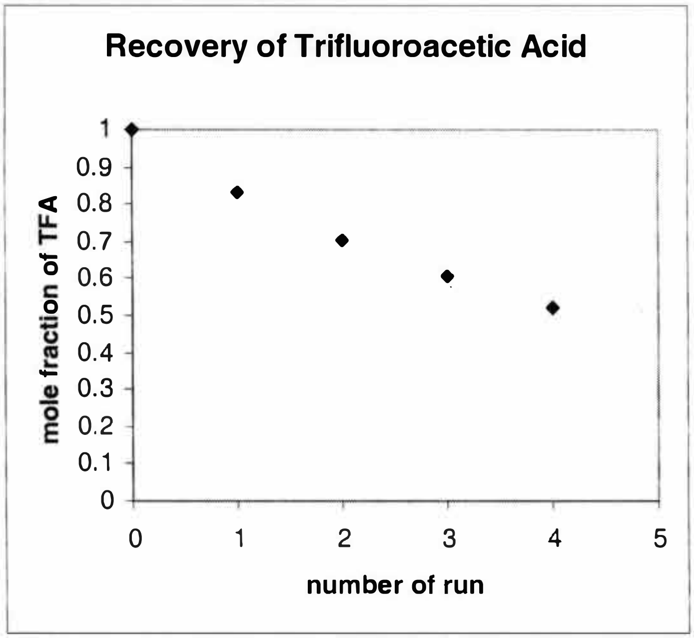


Figure 12. Recovery of Trifluoroacetic Acid.

of product was then determined by GC-MS analysis. The results are presented in Figure 12. It shows that the minimum amount of TFA needed to obtain ~70% yield p-MTPM was 0.2 mL. When 0.06 mL of TFA was used, the yield of p-MTPM dropped off significantly. Therefore, when using this experiment to teach the tenets of green chemistry, two possible experiments could be used. As described above, excess catalyst can be used and the concept of recycling can be illustrated. Alternatively, minor amounts of catalyst could be used, for example 200 microliters, to demonstrate the use of an efficient catalyst. This would be compared to the high amounts of catalyst (H_2SO_4) used and waste generated in the conventional synthesis.

The quantities of the materials used and the waste generated (which are primarily the auxiliaries in the conventional synthesis) of each method presented should be pointed out to the students and then compared to the respective yields. Secondly, an atom efficiency calculation of the reactions (Table 9), including auxiliaries, should be performed which will drive home the point of the unnecessary generation of waste. Thus, in an very simple experimental procedure and with relatively minimal concept lecturing, the students would clearly appreciate the developing concepts of green chemistry.

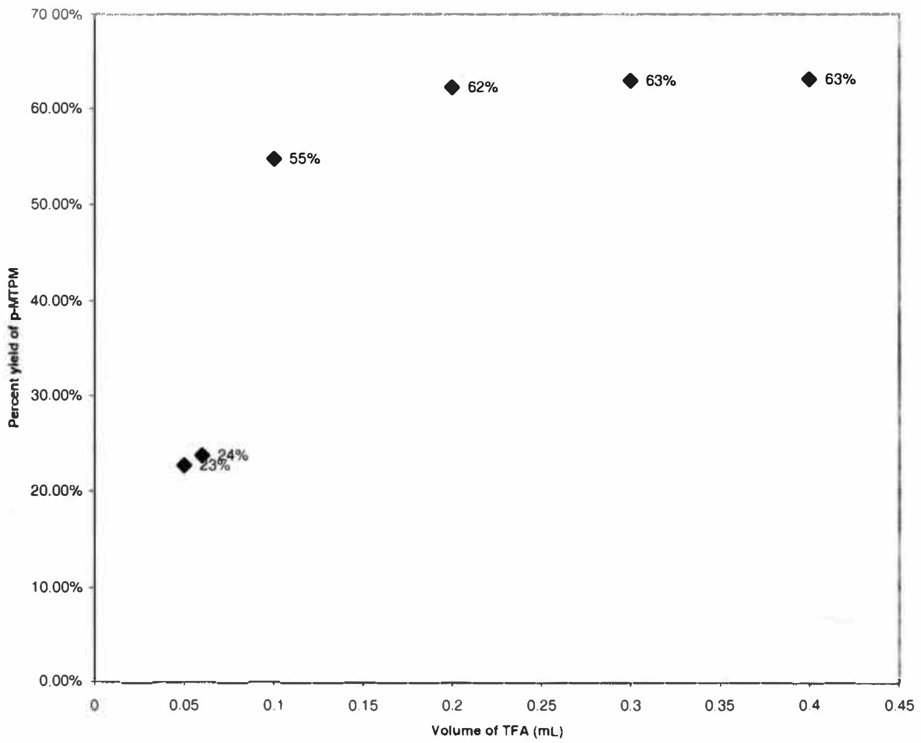


Figure 13. Percent Yield of p-MTPM Versus Volume of TFA.

Table 9

Atom Efficiency Calculation of the Reactions

Atom accounts in Friedel-Crafts alkylation using concentrated sulfuric acid and acetic acid

Element	Fate	Atom utilisation
Carbon	Products and byproducts	Up to 100%
Hydrogen	Products, by-products and waste	<< 100%
Sulfur	Waste	0%
Oxygen	Waste	Down to 0%

Atom accounts in Friedel-Crafts alkylation using trifluoroacetic acid

Element	Fate	Atom utilisation
Carbon	Products and byproducts	Up to 100%
Hydrogen	Products, by-products and waste	<< 100%
Fluorine	Recover for next run	83%
Oxygen	Recover for next run	83%

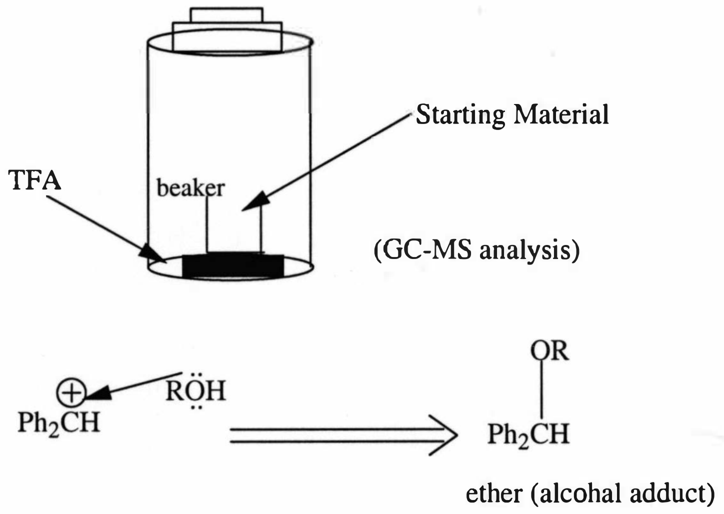


Figure 14. High Pressure CO_2 Experiments Using a Small Beaker to Separate the Alcohol and Anisole Reactants From the Acid Prior to Charging the Reactor With CO_2.

CONCLUSIONS

In this work, we first presented isolated product yields of the FC alkylation reaction between triphenylmethanol and anisole performed under supercritical CO_2 and subcritical CO_2 reaction conditions. It was clear from visual observations (high pressure optical cell) that at the highest CO_2 fluid density conditions used in this investigation, the FC reaction occurred under homogeneous conditions. Unfortunately, under these conditions the product yield was low, ~3-4%. Mixed results were obtained using the other alcohols as carbocation precursors, and unfortunately, none were found to be suitable for use under SCF conditions. The preparative experiments performed using Ph_3COH under neat liquid conditions, see Table 7, demonstrated that FC reactions can be performed very efficiently using neat reaction conditions when TFA is used as the FC catalyst. That observation led us to consider using the neat Ph_3COH /anisole /TFA system as an educational tool to teach undergraduates some of the tenets of green chemistry.

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