Development of a Field-Ready Colorimetric Test for the Identification of Synthetic Cathinones

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Abstract

In recent years, the number of synthetic cathinone derivatives has increased dramatically. The effects of the extended use of these compounds is not well understood, leaving health professionals and law enforcement at a severe disadvantage when it comes to addressing global cathinone abuse. There is currently no viable field-ready presumptive test for the identification of all synthetic cathinone derivatives due to their rapid modification and proliferation in clandestine labs. Here, a novel colorimetric test for the detection of synthetic cathinones using transition metal salts is discussed. The test targets the ketone functionality present on all synthetic cathinone derivatives. No visible color change was observed when the target drug molecule was added to the aqueous metal solutions. Further research into the possible use of catalysts or other metal compounds would be beneficial. Namely, catalysts capable of facilitating metal alkoxide formation.

Introduction

For the last several decades, the abuse of illicit drugs for recreational purposes has been a costly problem for local, national, and international drug enforcement agencies.[1,2] Amphetamines, cannabinoids, cocaine, and opioids account for the majority of these illicit compounds abused around the globe annually.[1] However, the development of novel derivatives of these drugs is surprisingly low. Other than the recent emergence of dangerous fentanyl-like compounds and synthetic cannabinoid variants, there have been no major changes to the chemical structure of the most widely abused compounds: cocaine, heroin, and methamphetamine.[1,3] This is extremely advantageous to law enforcement and health officials, as the techniques used to identify, analyze, and medically treat the use of these compounds are well documented and widely available. For example, the Marquis test, a cheap colorimetric test used to determine the presence of opiates, has been used since 1896 and can be found in most forensic laboratories.[4]

On the other hand, the identification of new psychoactive substances (NPSs) has become an increasingly difficult problem for law enforcement. NPSs are a broad classification of novel synthetic or "designer" drugs, often modified derivatives of naturally occurring compounds.[2,5] Most NPSs were not designated as controlled substances when the United Nations convened in 1961 and 1971 to discuss the global narcotics market.[6] At these conventions, UN members outlined which substances posed the largest risk to human health and should therefore be regulated at an international level. Thus, many of these substances were marketed as legal alternatives, often referred to as "legal highs," which dramatically increased their popularity across Europe and the United States.[5-7]

The major issue is that most NPSs elicit similar physiological responses to other illegal stimulants, namely cocaine and opioids, while being more readily available and cheaper.[5-7] Due to

the lack of regulation, clandestine labs were able to focus on developing more potent synthetic substances in order to increase their popularity among recreational drug users. A direct result of their rapid proliferation is that the adverse health effects of these compounds is not greatly understood, posing serious challenges for law enforcement and health professionals alike. Namely, there is a lack of both detection and treatment techniques for these novel substances. This greatly diminishes the ability for medical and law enforcement agencies to deal with the major implications of substance abuse (medical emergencies, legalities, etc.). Of all the NPSs, synthetic cathinones are regarded as the most prominent and dangerous.[2,7]

Synthetic cathinones, more commonly known by the street name "bath salts," are chemical analogues of the naturally occurring compound, cathinone, found in the khat (*Catha edulis*) plant. Chemically, cathinone is similar to amphetamine with the exception of an added β-keto group in relation to the amine (see **Figure 1**). Synthetic cathinones were first used for medicinal purposes in the late 1930s but have since become popular for their psychoactive and stimulant properties.[7]

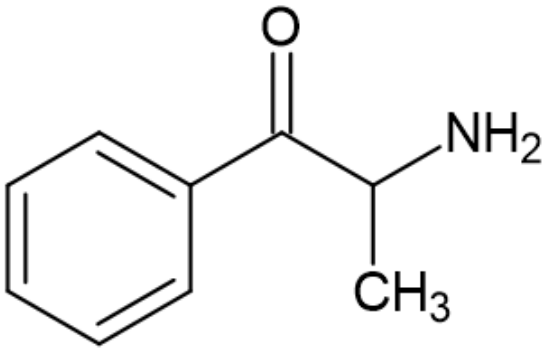


Figure 1. Molecular structure of cathinone.

In 2005, methylone became the first synthetic cathinone reported for recreational use to the European Monitoring Centre on Drugs and Drug Addiction.[6] By 2011, methylone and mephedrone, both of which had just been classified as schedule I drugs in the U.S. in October of

the same year, were found in over 30 European countries.[8] As of 2015, a staggering 33% of all NPSs seized in Europe were novel synthetic cathinones, and they accounted for over half of all hospital emergencies related to NPSs.[9]

In the United Kingdom, cases relating to cathinone toxicity increased from 0 to 600 between 2009 and 2010.[8] Similarly, the number of calls to the U.S. poison control center related to synthetic cathinone abuse increased from 304 in 2010 to 6,138 in 2011.[10] Since then, the number of cathinone related overdoses and intoxications has increased dramatically.[5] As such, extensive funding has been provided by the U.S. Department of Justice and National Institute of Health in order to combat this growing problem, specifically with regards to detection and medical treatment. When cathinones first appeared on the global market, forensic technicians were left at a disadvantage due to the lack of techniques needed to properly identify the specific molecule present.[5] Looking at the chemical structure, most synthetic cathinones appear very similarly. However, the small distinctions can completely alter the chemical reactivity and physiological response in the body. This means it is extremely important to identify which synthetic cathinone is present in order to determine the proper course of action.

The most obvious choices for researchers were gas and liquid chromatography (GC/LC) coupled with mass spectrometry (MS).[5,11] GC-MS and LC-MS are the pinnacle of chemical identification techniques and are employed in analytical labs around the world. In short, both techniques use differences in polarity between the target analyte (in this case, synthetic cathinones), and a separatory column to isolate the target. Once separated, the analytes are ionized and pushed through a strong electromagnetic field which separates ions based on size. Although these methods are extremely useful in most settings, there are certain disadvantages specifically in regard to cathinone/illicit drug detection in the field. Most notably, these instrumental techniques

are fairly expensive, time consuming, and do not support high-throughput analysis.[5] Time and portability are crucial for forensic analysis, as most illegal drug seizures will not occur within a laboratory. Furthermore, there are several publications which highlight the extremely labile nature of cathinones at high temperatures.[9,11,12] In GC-MS, cathinones are prone to extensive fragmentation at these temperatures, which reduces the accuracy of the results.

One promising option involves the use of presumptive colorimetric tests. Colorimetric tests, or spot tests, have been used to identify the presence of a target chemical for over 100 years. Today, forensic scientists and crime scene investigators utilize several different spot tests for the detection of illicit compounds. Unlike other instrumental methods, color tests are rapid (results usually within a minute), inexpensive, easy to carry, and require little training from the user.[4,5] A drug sample is typically dissolved in a reagent solution, and the produced color is compared to a reference chart. Some tests are specific to one drug type, while others can be used to detect multiple drugs. For example, the Scott's reagent test is used solely to identify the presence of cocaine, while the Marquis test is able to identify opiates, amphetamines, and MDMA (ecstasy) based on the color produced.[4] Additionally, colorimetric tests can be highly specific, requiring only micrograms of the drug to be present in order to elicit a desired response.[4] Furthermore, advancements in technology have been able to reduce one of the major disadvantages of color tests: subjectivity from human vision. Everyone perceives color differently, and ambient light may change from location to location. This could lead to false positives or inaccurate readings. However, smart phone apps have been developed which can quantitatively measure a color sample, thereby greatly improving the accuracy of the result.[4]

As of 2020, there are a few commercially available color tests which claim to detect synthetic cathinones. Unfortunately, these tests are often hazardous, not specific towards

cathinones alone, or do not fully screen for the most common synthetic cathinone derivatives.[13] For example, researchers have noted the Marquis test can react with some forms of synthetic cathinones containing a methylenedioxyl group (like MDPV), but yields no result with other forms of the drug.[7] One of the biggest difficulties with cathinones is their rapid evolution and changeability. New variations of cathinones are being developed at a dangerously high rate each year.[2,6] This is partly due to the facile modification of the cathinone substructure. Modifications to the amine, α-carbon, and aromatic ring are common and can easily be done with minimal knowledge of chemistry (see **Figure 2**). Substituents such as halogens, alkyl groups, cyclic rings,

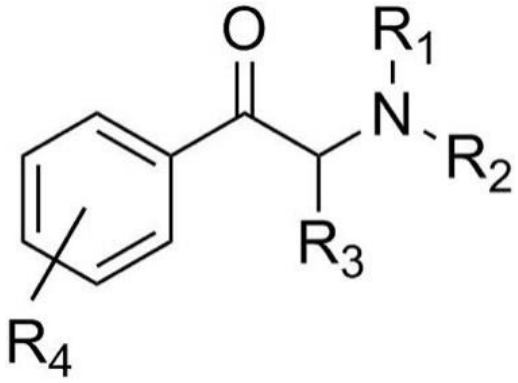


Figure 2. Cathinone structure with possible sites of modification, labeled R_1-R_4

and ethers are some of the most common groups and can be added in a variety of combinations. Thus, a wide range of substituent modifications is possible, resulting in a serious analytical challenge for forensic investigators.[7]

The major issue limiting spot tests are their current inability to identify *all* synthetic cathinones on the drug market. In the past five years, only a handful of publications have outlined possible color tests for synthetic cathinones. However, none of these tests were able to positively identify all cathinone derivatives examined. Some even required extra steps which may not be suitable for field testing, such as heating.[4,5,13] The development of a cheap, safe, and reliable universal spot test, capable of quickly identifying the presence of any synthetic cathinone during

a drug seizure or medical emergency, is imperative for combatting this issue. Such a spot test would not necessarily need to identify the specific cathinone present, but would need to differentiate cathinone derivatives from other illicit compounds. Once a drug is determined to be a derivative of cathinone, law enforcement or medical personnel can respond accordingly.

Colorimetric tests can generally be broken down into two major categories: organic and inorganic based. The former usually involves the exploitation of aromaticity, conjugated pi-systems, or dyes to produce a noticeable color change.[14] For example, the Zimmerman reagent is a mixture of 2,4-dinitrobenzene, methanol, and potassium hydroxide capable of detecting compounds that contain a β-amino ketone functionality. The α-carbon proton of a β-amino ketone is fairly acidic, and is easily deprotonated by a strong base. The resulting carbanion is extremely nucleophilic and reacts with the electron deficient 2,4-dinitrobenzene to produce a green-blue product.[14] Inorganic based tests instead use transition metal complexes to elicit a desired color change. Due to the half-filled nature of the d-orbital, electronic transitions between ligands and the central metal can occur (also called a ligand to metal charge transfer or LMCT), resulting in the vibrant colors exhibited by transition metal compounds. Some common examples of inorganic based colorimetric tests are the Scott reagent (cobalt(II) thiocyanate) and Chen-Kao test (cupper(II) sulfate). In these presumptive tests, the target drug molecules act as ligands, binding to the transition metals which induces a LMCT.

When designing a colorimetric test, it is necessary to identify which functionality present on the desired molecule will be targeted. Ideally, this functionality is fairly reactive and not commonly found on many compounds. For example, the previously mentioned Zimmerman reagent targets β-amino ketones specifically, while the ferric chloride test only reacts with phenolic alcohols.[14] A major issue with synthetic cathinones is the multitude of functional groups present

on the various derivatives. If, for example, one test was capable of targeting the primary amine present on the cathinone molecule, then synthetic derivatives that contain a secondary or tertiary amine would not react. Interestingly, there is one functional group present on all synthetic cathinones that could theoretically be targeted: the ketone. All synthetic cathinone derivatives possess an aryl ketone, but there is very little research discussing the identification of cathinones via the ketone.[12] This is because ketones are generally stable at standard conditions, and derivatization of the carbonyl can be difficult without altering pH or temperature which might affect the integrity of the test.[12] To possibly circumvent this problem, the carbonyl could be made more reactive through a reduction reaction.

The reduction of a ketone to its corresponding alcohol is a fundamental reaction of organic chemistry. Such reactions are commonly used in the pharmaceutical and materials industries, where transformative chemistry is extremely important.[15] By reducing a ketone to an alcohol, the oxygen atom becomes less restrictive and more readily available to react with other molecules due to its increased polarity. This is extremely useful for the formation of metal-oxygen (M-O) bonds, where the literature suggests that M-O bonds are stronger and more favorable as the electronegativity of the oxygen atom increases.[16] If, for example, the formation of an M-O bond between a reduced synthetic cathinone and transition metal induces a LMCT, then a colorimetric test can be created to exploit this.

In this study, a procedure for the reduction of a cathinone-like analogue is discussed and its interaction with various transitional metal salt complexes are reported. The purpose of this analysis is to determine the efficacy of reducing synthetic cathinone derivatives in the presence of a transitional metal. Ideally, the formation of a M-O bond will induce a LMCT capable of producing a noticeable color change. The proposed test would have two major steps: 1) the

reduction of the target ketone into its subsequent alcohol and 2) the addition of this alcohol to a transition metal solution.

Results and Discussion

Two-Step Test

The initial aim of the project was to create a novel presumptive spot test for the identification of synthetic cathinones. As previously stated, the targeted functionality of the cathinone structure would be the aryl ketone, and an inorganic based transition metal solution would be used to produce the desired color change. There is very little in the literature that discusses the reduction of cathinone, and even less that discusses the interaction between cathinones and transition metals. In a study by Philp et al[13], they propose a color spot test for the detection of cathinone using a copper neocuproine solution. However, the cathinone does not form a M-O bond with the copper, but instead acts as a reducing agent changing the metal to a 1+ from a 2+ oxidation state in the presence of heat. While this is not direct proof that cathinone derivatives will form a coordinate covalent bond with a metal, it does suggest that synthetic cathinones can react with metal centers to produce certain desirable color changes.

Acetophenone was chosen as an analogue to cathinone because it was readily available, cheap, and similar in structure to cathinone. Although acetophenone does not possess the amine moiety like cathinone, it is an aryl ketone which is the necessary functionality for this specific test. When designing the test, it was necessary to ensure that all steps were performed at room temperature. This was done to ensure the test can be used in the field without the need for heat or another catalyst. There are several common methods of reducing ketones to alcohols, namely through the use of reducing agents such as sodium borohydride ($NaBH_4$) or lithium aluminum

hydride (LAH).[17] LAH is generally considered a stronger reducing agent and is often used to reduce far less reactive groups such as esters. Therefore, sodium borohydride was chosen because it is more specific to ketones, cheap, and a common reagent found in many laboratories. Additionally, the reaction between $NaBH_4$ and ketones is exothermic and there are several studies that suggest it is a viable reducing agent at room temperature.[18-19]

The procedure followed for the reduction of acetophenone was based off a generic organic undergraduate methodology and can be found in the **Methodology** section below. The product of the reaction was characterized using Infrared Spectroscopy (IR) and Proton Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR). The reduced product, 1-phenylethanol, was a clear oily liquid which matched descriptions found in the literature.[20] The use of IR was chosen since the reduction of a ketone to an alcohol can clearly be determined through the disappearance of a sharp peak around 1700 cm^{-1} (indicative of a carbonyl) and the appearance of a broad peak around 3000 cm^{-1} (indicative of an alcohol). The IR data can be seen below in **Figure 3**. As predicted, the appearance of a broad peak at 3332 cm^{-1} was matched by the lack of a strong peak around 1600 – 1800 cm^{-1}.

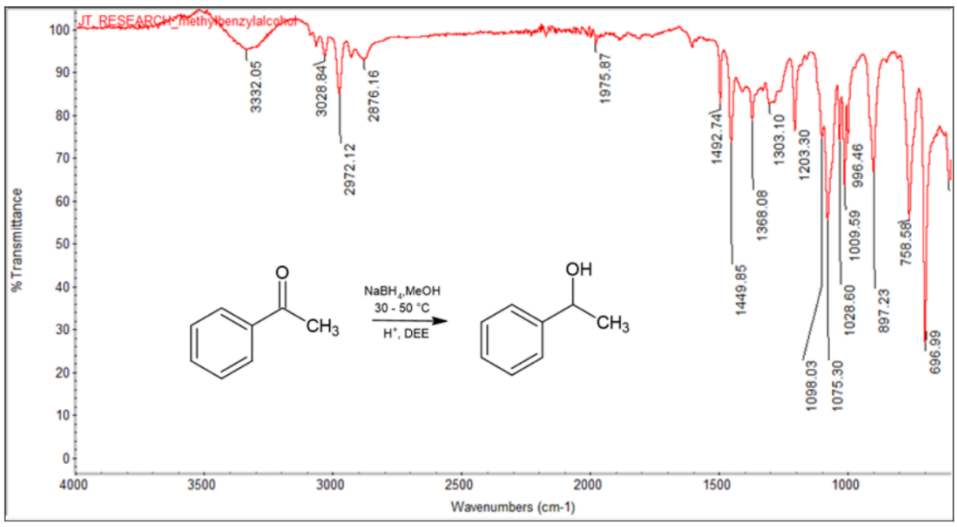


Figure 3. IR spectra of 1-phenylethanol. Lack of carbonyl peak suggests reduction of acetophenone was successful.

Additionally, small peaks between 2800 cm^{-1} – 3100 cm^{-1} indicate the presence of aromatic carbon – hydrogen bonds, which would be expected from 1-phenylethanol.

^{1}H NMR analysis was performed in conjunction with IR to confirm the presence of 1-phenylethanol. The ^{1}H NMR spectra can be seen in **Figure 4** below. There are six unique proton environments on 1-phenylethanol, labeled A-F on the molecular structure of 1-phenylethanol

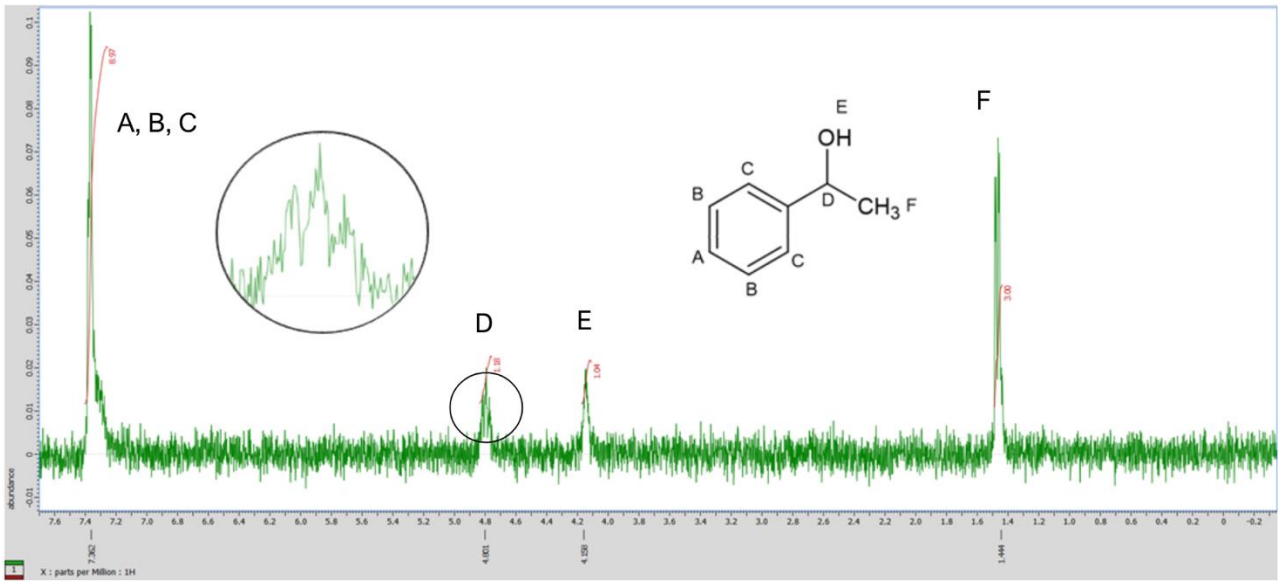


Figure 4. ^{1}H NMR spectra of 1-phenylethanol with labeled molecular structure.

included in **Figure 4**. The results of the analysis are as follows: 1-phenylethanol: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.444 (d, 3H), 4.198 (s, 1H), 4.801 (q, 1H), 7.392 (s, 9H). While six unique environments were predicted, only four peaks were present. Overlap of the aromatic protons is likely to blame and is a common occurrence due to the similarities between these environments on 1-phenylethanol. The integration value of 8.97 for this peak is also higher than expected due to overlap with the solvent peak. Chloroform-d produces a singlet peak around 7.26, which has likely merged with peak A, B, C to raise the integration value. Other than this anomaly, the remaining

peaks match the predicted shifts, splitting, and integration values well. Peak D is a quartet shifted further downfield than usual C-H protons due to its proximity to the aromatic ring and alcohol. The neighboring methyl is responsible for the splitting pattern observed. The alcohol proton is a singlet around 4 ppm, while the methyl is a doublet furthest upfield.

Once formation of the reduced product was confirmed, addition of the 1-phenylethanol to transition metal solutions was conducted. As there was no basis for comparison for this step (no previous literature), this step essentially consisted of trial-and-error analysis. Transition metal salts were chosen based on four major categories: solubility, lability, location on periodic table, and availability. Based on other inorganic colorimetric tests, period 4 transition metals were chosen as they are the most common. These include scandium, titanium, vanadium, manganese, iron, cobalt, nickel, copper, and zinc. With the exception of zinc, these transition metal salts exhibit a wide range of colors that are well documented. Furthermore, most of the complexes of these metals are water soluble and extremely cheap (compared to 5^{th} and 6^{th} period transition metals), which makes them prime candidates for aqueous colorimetric testing. **Table 1** below lists the 10 transition metal salts studied, their solubility in water, and their color in solution.

TM Salt	Solubility (in water)	Color
Cobalt(II) nitrate	soluble	dark red
Cobalt(II) sulfate	soluble	red
Cobalt(II) chloride	soluble	red
Iron(III) nitrate	soluble	yellow
Iron(III) chloride	soluble	yellow
Nickel(II) sulfate	soluble	turquoise

Copper(II) acetate	soluble	blue
Copper(II) nitrate	soluble	light blue
Copper(II) chloride	soluble	green-blue
Copper(I) bromide	slightly soluble	moss green

Table 1. Transition metal salts explored. Their solubility and color in aqueous solution is listed. See **Appendix 3** for visuals

The procedure followed to create these solutions can be found in the **Methodology** section below. The aqueous solutions were placed in a labeled test tube, and a few drops of 1-phenylethanol were added. Upon addition, the solutions were monitored for five minutes, and visual observations were made every 30 seconds. After five minutes, 9 out of the 10 solutions had no visible color change. Likely, no reaction between the 1-phenylethanol and aqueous metals was occurring due to the lack of a catalyst. As reported in the literature, metal alkoxide synthesis generally requires the use of reagents or heat to facilitate the M-O bond formation. Bellow et al.[21] reported a synthesis strategy for iron alkoxide complexes which required the use of catalytic thallium hexafluorophosphate($TlPF_6$). Similarly, the Bellow research group also reported the use of $TlPF_6$ and heat as a catalyst in the synthesis of manganese, copper, and nickel alkoxides.[22]

Interestingly, the copper(I) bromide solution became a brown color upon instant addition of the 1-phenylethanol. Initially, this was believed to be the result of a M-O bond formation between 1-phenylethanol and the copper metal. However, the presence of bubbling and a black precipitate in the tube suggested some type of unwanted redox reaction was likely occurring. Upon researching, it was discovered that in the presence of $NaBH_4$, some hydrated metal halides can be

reduced to form metal borides and borates. The Glavee research group[23] showed how aqueous nickel and copper atoms are reduced in the presence of borohydride. The reaction between copper(II) chloride and $NaBH_4$, for example, produced metallic copper, hydrogen gas, and boric acid. As reported by Glavee et al., the metallic copper and boron side products appeared as black precipitates, and the formation of bubbling was indicative of hydrogen gas formation.[23]

To determine if remaining $NaBH_4$ was the cause for the brown color change, the reduction of acetophenone was performed again and extra care was taken to ensure no $NaBH_4$ remained in the final product ($NaBH_4$ was measured as the limiting reagent, the product was extracted with diethyl ether (DEE) x5, and the DEE extracts were dried over sodium sulfate for 30 min). The synthesis of 1-phenylethanol was again confirmed using IR and ^1H NMR, and the same procedure for addition to the aqueous metal solutions was followed. Similar to the previous trial, the same nine solutions failed to produce a noticeable color change. Once the product was added to copper(I) bromide, no brown color change was observed either. Not only did this confirm that 1-phenylethanol had not reacted with any of the transition metals, but it also shed light on a major flaw in the test design. For the reduction reaction, the acetophenone was added to a $NaBH_4$ solution and then isolated with DEE via a liquid-liquid extraction. While such an extraction is easy to perform in lab, it would be difficult to ensure the reduced drug is transferred to the DEE layer in the field. If there is any remaining reducing agent, it could interfere with the transition metal solution to produce an undesirable color change. Such a color change could result in false positives or negatives, which is a major limitation of any colorimetric test.

Sodium Nitroprusside Test

This discovery meant that the proposed two-step test (reduction followed by addition to transition metal solution) would not be viable for a field spot test. To avoid this issue, the proposed test needed a rework to ensure that it could be used outside of a laboratory. One possible route was the modification of a known test for the detection of ketones, instead of trying to develop a completely novel test. While there are not many ketone specific colorimetric tests, one promising option involved the use of sodium nitroprusside (SNP).

Sodium nitroprusside is an inorganic complex that consists of an iron center surrounded by five cyanide and one nitrosyl ligand, with the formula $Na_2[Fe(CN)_5NO]$. Commercially, sodium nitroprusside is used for the detection of ketones in urine, and test strips containing a SNP reagent solution are available at most pharmacies. In an alkaline solution, SNP reacts with ketones to produce a deep red/purple color. While the mechanism for this reaction is not well documented, it is believed that the ketone is deprotonated at the α-carbon similar to the dinitrobenzene test discussed previously. The subsequent carbanion then reacts with the electrophilic nitrosyl ligand, producing a compound with the desired color change. There is a severe lack of previous research discussing the SNP test for ketones; interestingly, however, SNP is well documented as a forensic tool for the detection of amines. Simon's Reagent is a mixture of SNP, acetaldehyde, and sodium carbonate, and is used for the detection of primary and secondary amines.[14] This mechanism is better understood, and the nitrosyl ligand plays a key role similar to the predicted mechanism for the reaction with a ketone. With the Simon Reagent, a Schiff base is formed between the target amine and acetaldehyde which reacts with the nitrosyl group on SNP to form the Simon-Awe complex (blue color). Since SNP has already shown promise as a forensic spot test with amines, it seemed a viable option for a new test aimed at targeting ketones.

Unfortunately, due to the Covid-19 pandemic, the process of ordering and shipping sodium nitroprusside was far lengthier than expected. In general, domestic shipping services experienced huge delays due to the increased number of shipments caused by the nationwide quarantine. As such, the SNP never arrived, and the test could not be performed. Ideally, a 10% SNP solution would be used, and the target ketone could be added to this solution followed by the dropwise addition of a base to produce the red color change (see **Figure 5**). This procedure was adopted

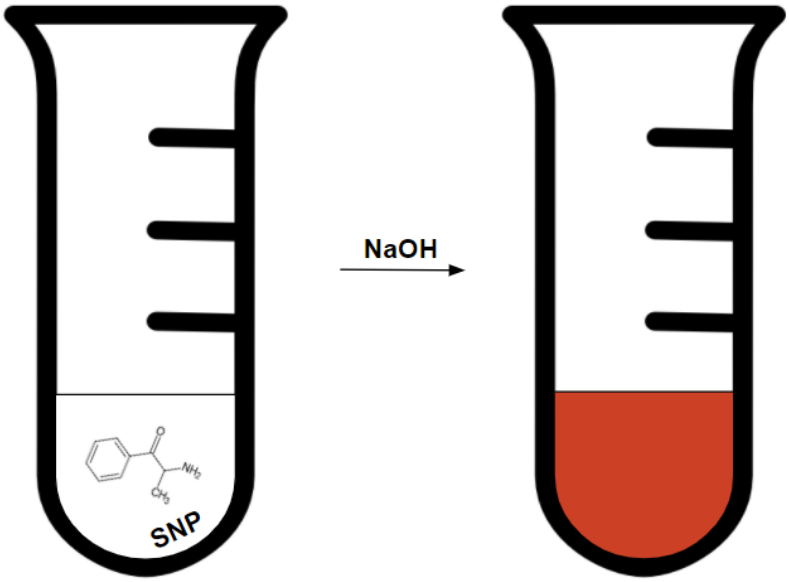


Figure 5. Schematic for hypothetical cathinone colorimetric test using sodium nitroprusside. Cathinone is deprotonated at the α-carbon and reacts with SNP to produce a red color.

based on similar tests found in the literature.

Conclusion

In sum, a variety of transition metal solutions were examined as possible colorimetric tests for the identification of synthetic cathinones. Due to the varying modifications on each derivative of cathinone, designing a single test capable of detecting all variants is extremely difficult. Targeting the ketone functionality seems to be a promising avenue, as all derivatives contain this group. While none of the transition metal solutions produced a color change, the addition of a catalyst could possibly circumvent this problem. If given the time, it would have been useful to see what, if any, catalysts could possibly facilitate the production of a M-O bond. Additionally, future work could involve the use of sodium nitroprusside. Although it is currently used for the detection of amines, it shows promising forensic applications as a method of identification for ketone-containing compounds. Despite being used commercially for ketone detection in urine, there seems to be little research into its use beyond this application.

Methodology

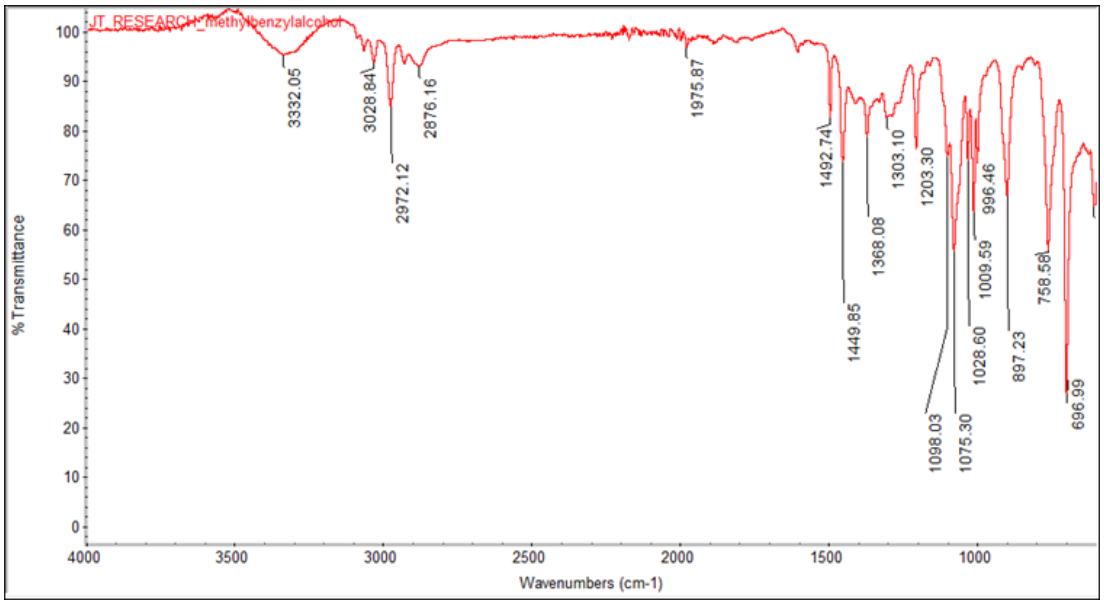
Reduction of acetophenone

To a 25 mL RBF, 10 mmol of sodium borohydride is added along with 10 mL of 95% ethanol. A magnetic stir bar is added, and the solution is stirred until all of the sodium borohydride is dissolved. In a separate container, 25 mmol of acetophenone is measured. The acetophenone is added dropwise over a period of 30 min. The reaction is exothermic, so addition was slowed in order to keep the temperature between 30 – 50 ℃. Once the addition was complete, the solution was allowed to reach room temperature. Then, ~3 mL of 6M HCl was added. The solution was extracted with 5mL of diethyl ether x3. The organic layers were combined and dried over sodium sulfate. The solvent was evaporated off using a rotary evaporator and the product was characterized using IR and NMR.

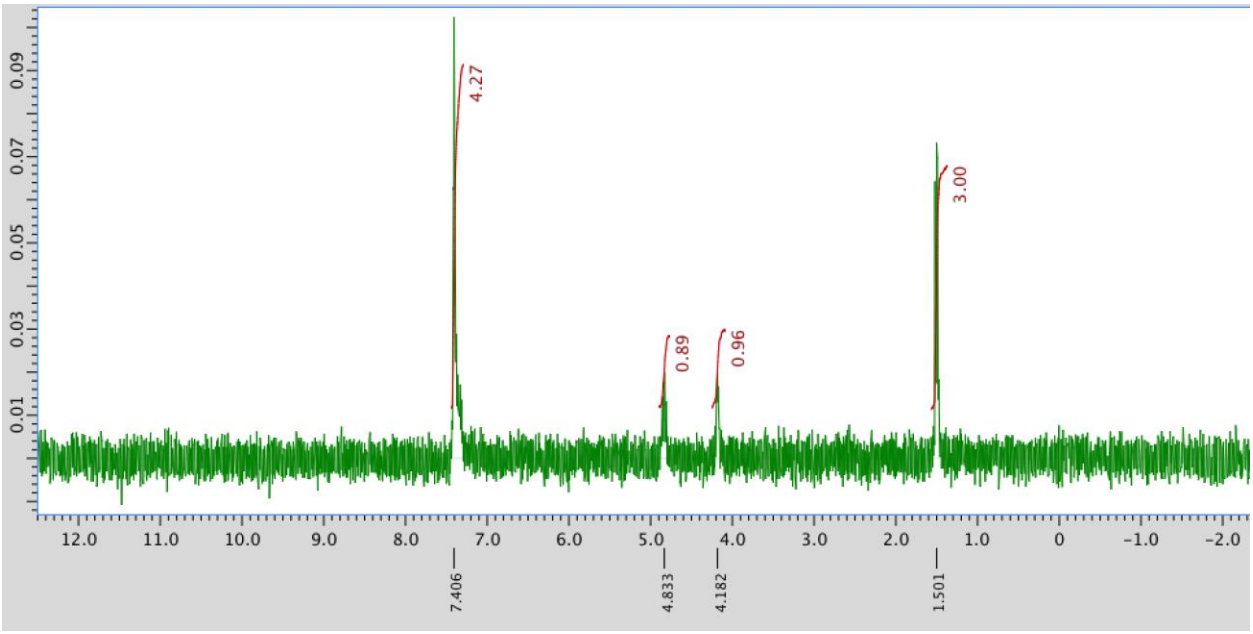
Creation of transition metal solutions

To a 50 mL flask, 0.5 g of transition metal salt were added along with 30 mL of deionized water. The solutions were stirred until all of the solid salts were dissolved.

Appendix

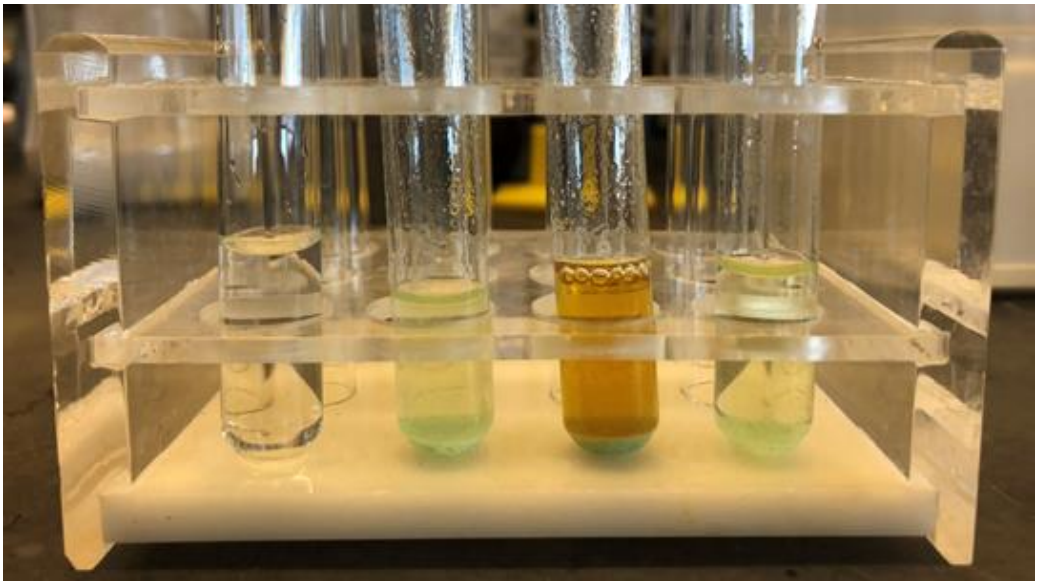


Appendix 1. IR spectra of reduced product, 1-phenylethanol. Prominent peaks are observed at 3332, 3028, 2972, and 2876 cm^{-1}



Appendix 2. ^{1}H NMR spectra of 1-phenylethanol. ($CDCl_3$, 300 MHz): δ 1.501 (d, 3H), 4.182 (s, 1H), 4.833 (q, 1H), 7.406 (s, 5H)

Appendix 3. Eight out of ten transition metal salts analyzed. From left to right: Cobalt(II) nitrate, cobalt(II) sulfate, cobalt(II) chloride, iron(III) nitrate, iron(III) chloride, nickel(II) sulfate, copper(II) acetate, copper(II) nitrate. Not pictured: copper(II) chloride and copper(I) bromide.



Appendix 4. Addition of 1-phenylethanol with copper(I) bromide. From left to right: 1-phenylethanol in DI water, CuBr in DI water, 1-phenylethanol and CuBr in DI water, acetophenone and CuBr in DI water. The brown color change was determined to be leftover $NaBH_4$.

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