SYNTHESIS AND CHARACTERIZATION OF A NEW GENRE OF CS-COMPOUNDS

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ABSTRACT

Three groups of organic compounds are currently being used as riot control and crowd management agents. Included in these three groups are: ω–chloroacetophenones (CN), benzylidene malononitriles (CS) and dibenzo-oxazepines (OR) (Fig. 1). o-Chlorobenzylidene malononitrile (1) is the most popularly used non-lethal agent in riot control situations and military exercises. Since this compound contains chlorine, it is not environmentally safe. With a view to improve its properties and enhance its effectiveness, a new group of CS compounds containing fluorine have been synthesized using micro-wave exposure and new inorganic catalysts in neat reactions. The synthesis and characterization of a novel group of CS compounds are described herein.

INTRODUCTION

Since World War I, three groups of organic compounds namely (**CN, CS** and **OR**) have been used to cause temporary incapacitation and have found application in crowd control and management situations, though prior to this they were employed as CW agents. The latter activity has been banned [1]. Of the three groups, two groups namely the CN and OR, seem to have fallen out of grace and the CS compounds have almost completely replaced the CN. The CS compounds are primarily used as riot control and anti-personnel agents and in military training exercises and testing of the protective masks. The most commonly used crowd control agent is o-chlorobenzylidene malanonitrile (**1**) [2]. Recently, compound **1** was used in copious amounts by law enforcement authorities in Seattle (WA) during the meeting of the World Trade Organization to control and manage disruptive activities of the unruly crowds. The CS are internationally used as tear gas agents. Sweden employs compound **1** (**Fig. 1**), under the trade name **K 62**, in military exercises and testing of the protective masks. In low concentration, the CS compounds primarily act as irritants and temporary incapacitants by eliciting and inducing various physiological effects including skin irritation, copious flow of tears, running nose, coughing, dizziness, etc [3]. In high concentrations, they cause nausea and vomiting. The median concentration for respiratory effects is said to be 12~20 mg/m^3, while for eye effects it is 1~5 mg/m^3. The onset time for maximum effects is 20~60 seconds and the duration of time is 5~10 minutes after the cessation of exposure [4]. The parent compound (**1**) exhibits LD_{50} in rats 28 mg/kg, i.v. rats 48 mg/kg and i.p. LC_{50} in rats 88,480 mg/min/m^3 [5a]. Comparative toxicological studies of CS and CN have been described [5a]. Also, the toxicological profile of CS has been published [5b]. At room temperatures, these compounds are colorless stable solids and possess low vapor pressure. The CS compounds have a half-life of 15 minutes and are readily removed by water at pH 7. **Table 1** shows the threshhold concentrations [TC_{50}] and incapacitating concentrations [IC_{50}] values in mg/m^3. [4].

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With a view to make the CS compounds environmentally more benign and safe and biologically more effective and potent, the synthesis of a new groups of CS compounds containing fluorine and fluorine containing moieties instead of chlorine has been accomplished under the influence of microwave exposure using new catalysts in the solid state. It is proposed to eventually synthesize a dozen or so new CS compounds containing

Figure 1: Common Crowd Management Agents
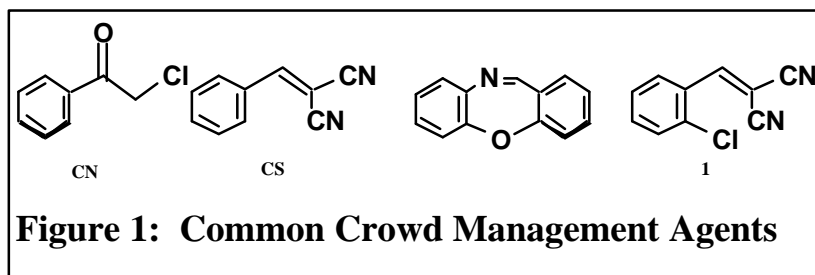
fluorine and to develop structure activity and property relationship profile to generate a computerized database for use in the unambiguous detection of their use. This paper describes the preparation and mass spectral characterization of the five such compounds.
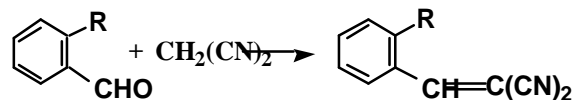
Table 1: Threshhold and Concentrantions of Non-lethal Incapacitants			
	CN	CS	CR
[TC$_{(50)}$] (eyes)	0.3	0.004	0.004
[TC$_{(50)}$] (respiration	0.4	0.023	0.002
[IC$_{(50)}$] values	20.5	3.6	0.7

Figure 2: New CS Compounds Cited in the text
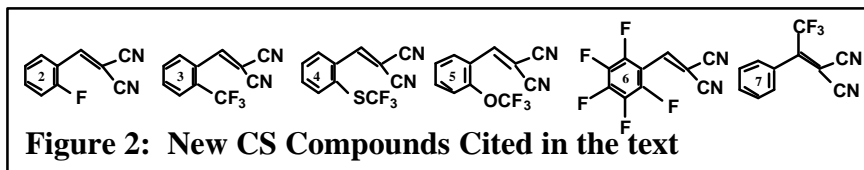
RESULTS AND DISCUSSION

Benzylidene malononitriles have attracted considerable attention recently for use as non-lethal chemical agents. Alkylidenation of the carbonyl compounds via the classical Knoevengel condensation of carbonyl substrates with compounds containing reactive methylene moieties is of general and wide application for creating carbon-carbon double bond. In general, this reaction is catalyzed by amines or ammonium salts [6]. Recently a variety of catalysts such as TiCl$_4$ [7a-b], CdI$_2$ [7c] alumina [7d-e], xeolites [7f-g], TeCl$_4$ [7h], silica [7i-j]; silica functionalized amines

2: R=F;   3: R=CF$_3$
4: R=SCF3; 5: R=OCF3

3: R=CF$_3$	CH$_2$(CN)$_2$	R-CHO	R-CO$_2$H	R-CHCl$_2$	R =C(CN)$_2$	=C(CN)$_2$
Dry freshly powdered alumina beads	11.4%	27.8%	1.5%	0.3%*	49.0%	-
Europium (lll) fluoride	2.2%	3.7%	2.9%	0.7%	90.0%	-
Hexafluoroammonium aluminate **	5.9%	19.5%	19.5%	-	62.0%	-
Piperidine		37.0%	4.0%		56.6%	0.4%
No catalyst					<8.0%	

* impurity present in the starting material, o-(trifluoromethyl)benzaldehye
** Two additional compounds were characterized from this reaction product, namely
o-(trifluoromethyl)phenol (0.6%) and o-(trifluoromethyl) ω–dicyanaomethylketone (10.8%)

[7k] and AlPO$_4$-Al$_2$O$_3$ complex [7l] have found application in the Knoevenagel reaction. Solvent free microwave reactions have also been employed for the synthesis of these compounds [8]. Instead of the carbonyl precursors the imines have been used and found to give similar results [9a]. Even amino acids have been stated to catalyze this condensation [9b]. The Knoevenagel condensation has been carried out diastereoselectively [10a-b] and enatioselectively [10c-d]. dilithio N-methanesulfinyl-p-toluidine [10e], tosylmethylisocyanide [10f], α-methoxyvinyllithium [10g], lithiated allylic carbamate [10h] and lithium bis(ethylene-dioxyboryl)methide [10l] have been employed as catalysts in the modified version of the Knoevenagel reaction. Recently, antimony based *in situ* generated catalysts have been employed to successfully alkylidenate steroidal ketones [11]. From the above narrative it seems that the Knoevenagel reaction can be brought about by any reagent! Two mechanisms have been advanced to explain and rationalize the formation of the reaction products [6a]. Over a century ago, Knoevenagel himself proposed that the Schiff base type intermediates are initially formed from the carbonyl compounds, which then go on to react with the reactive methylene moiety and yield the alkylidene derivative. Based on the observation that organic bases catalyze the reaction, Hann and Lapworth suggested that the organic bases generate carbanions from the reactive methylene group, which subsequently react with the carbonyl compounds to furnish β–hydroxyl compounds [6a, pp.213 - 15]. The latter compounds undergo dehydration to yield the end products of the reaction. The survey of the published literature indicates that both the mechanisms are operative. Our own results indicate that these mechanisms may be operating independently of each other.

With a view to developing synthetic methodology, microwave assisted synthesis of benzylidene malononitriles in the neat phase has been explored using new catalysts such as europium (lll) fluoride, ammonium hexafluoroaluminate and dried freshly powdered alumina beads. **Table 2** summarizes the results of the reaction of o-(trifluoromethyl)benaldehyde with malononitrile. Six

new benzyliedene derivatives containing fluorine and fluorine containing functional groups have been synthesized (**Fig. 2**) and characterized by their NMR and Mass Spectral data. The mass spectral fragmentation of the said six compounds is given in **Table 3**. What is unique about the present work is the characterization of two ω–dicyanoacetophenones, namely o-(trifluoromethyl)- and o-(trifluoromethylthio)-ω–dicyanoacetophenone. This suggests that the β–hydroxyl intermediates can also get oxidized by the catalysts to furnish the ω–dicyanoacetophenones. To the best of our information, this has not been observed in the Knoevenagel reaction before. Another interesting observation is that both o-fluoro- and o-(trifluoromethyl)benzaldehydes themselves are extremely powerful irritants and as such are readily amenable for use as CS compounds. Their effect is temporary and they can be conveniently washed off with copious amounts of water and soap. Secondly the melting points of o-(chloromethyl)- and o-(fluoromethyl)benzyledene malononitriles (**1** and **2**) are 95 – 96° and 118 – 19° respectively. This was somewhat unexpected. It was thought that the m.p. of compound **2** would be lower than that of compound 1. However, the melting points of

o-(chloromethyl)- and o-(trifluoromethyl)benzyledene malononitriles (**1** and **3**) are 95 – 96° and 48 - 49° respectively. This means that the vapor pressure of compound **3** is considerably lower than the popularly used CS agent. The microwave-technique described herein possesses a distinct advantage; in that the reactions can be carried without the use of any solvent and thus decreasing the generation and accumulation of hazardous laboratory waste. In addition, the reaction times can be dramatically reduced and the formation of side products minimized.

EXPERIMENTAL

Stoichiometric amounts of the respective reagents were mixed in glass vials or 5 ml ground joint round bottom flasks and stoppered, vigorously shaken on a vibro-mixer and heated in the microwave oven for a specified period. The reaction mixture was allowed to come to ambient temperature, the cooled product was filtered over cotton-wool, first analyzed by gas chromatography and then was subjected to GC-MS analysis. Mass spectra were obtained using a Finnigan TSQ-7000 GC/MS/MS equipped with a 30 m x 0.25 mm. i.d. DB-5 capillary column (J and W Scientific, Folsom, CA) or a Finnigan 5100 GC/MS equipped with a 15 m x 0.25 mm. i.d.Rtx-5 capillary column (Restek, Bellefonte, PA). The conditions on 5100 were: oven temperature 60-270° C at 10° C/min, injection temperature was 210°, interface temperature 230° C, electron energy 70 eV, emission current 500 μA and scan time 1 sec. The conditions on the TSQ-7000 were: oven temperature 60-270° C at 15° C/min, injection temperature 220°, interface temperature 250° C, source temperature 150°, electron energy 70 eV (EI) or 200 eV (CI) and emission current 400 μA (EI) or 300 μA (CI) and scan time 0.7 sec. Data was obtained in both the electron ionization mode (range 45-450 da) and chemical ionization mode (mass range 60-450 da). Ultrahigh purity methane was used as the CI agent gas with a source pressure of 0.5 Torr (5100) or 4 Torr (TSQ-7100). Routine GC analyses were accomplished with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m x 0.53 mm i.d. DB-5 column (J and W Scientific, Folsom, CA). The NMR spectra (^{1}H and ^{13}C) were recorded in CDCl$_3$ with TMS as the internal standard on a Varian VXR-400S spectrometer at 100 MHz and 376 MHz respectively.

Alumina Catalyzed Synthesis of o-trifluoromethylbenzylidene malononitrile: A mixture of stoichiometric amounts of o-trifluoromethylbenzaldehyde (43 mg) and malanonitrile (23 mg) and catalytic amount alumina oxide catalyst (20 mg) in small vial was exposed to microwave radiation for 1.5 minutes. The reaction was cooled to room temperature, treated with a small amount of chloroform, filtered to remove the catalyst and analyzed by GC and then by GC-MS.

The above reaction was repeated using different catalysts such as europium (lll) fluoride, ammonium hexafluoroaluminate, piperidine and silica. The results are summarized in **Table 2**. A similar reaction was carried out under identical conditions except that no catalyst was used in the condensation. Less than 8% of expected product was obtained. o-Fluoro-, o-(trifluoromethylthio)-, o-(trifluoromethoxy)- and pentafluorobenzylidene malononitriles (**2**, **4**, **5** and **6**, **Fig. 2**) were similarly prepared

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