

## Research Article

# Synthesis of new cyclo-hexane-1,3-dione derivatives by simple methods and their herbicidal activity

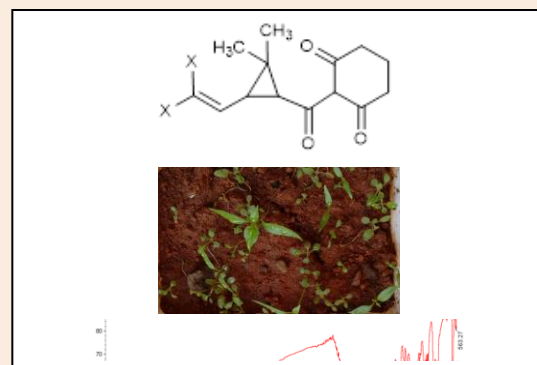
Rashmi S. Sharma and Anita S. Goswami-Giri\*

Chemistry Research Laboratory, Department of Chemistry, B.N.Bandodkar college of Science, Thane (W) MS India

**Abstract**

Novel {2-[(2,2-dimethylcyclopropyl)-carbonyl]cyclohexane-1,3-dione derivatives were prepared with 1,1-dibromoethene at the 3-position of the cyclopropyl ring. These compounds were synthesized with convenient methods. The synthetic method includes use of simple reagent like Dimethyl amino pyridine (DMAP), instead of the reported cyanide reagents, to bring about the rearrangement of the enol ester to the final triketone molecule. These compounds were characterized and their efficacy on the *Parthenium hysterophorous* weed was studied. These compounds belong to the triketone class of bleaching herbicides whose mode of action is the inhibition of *p*-hydroxyphenylpyruvatedioxygenase (HPPD), an enzyme present in the plants. These are a new class of natural product-derived herbicides.

**Keywords:** Triketone herbicides, DMAP, *Parthenium hysterophorous* *p*-hydroxyphenylpyruvatedioxygenase (HDDP)

**\*Correspondence**

Anita S. Goswami-Giri

Email: anitagoswami@yahoo.com

**Introduction**

The triketones are a novel class of bleaching herbicides whose mode of action [1] is the inhibition of *p*-hydroxyphenylpyruvatedioxygenase (HDDP), a key enzyme present in the plants. This enzyme breaks down the amino acid, tyrosine, into its components that are used by plants to create molecules that the plant needs. The structure of the triketones is derived from a natural phytotoxin produced by the bottle brush plant *Callistemon citrinus* [2,3]. The first of the triketone patents was published in 1986 [4]. The most frequently used triketones for weed control in maize cultivation are presented in Table 1.

**Table 1** Structures and names of some triketone compounds

Compound	Systematic name	Structure
<b>Sulcotrione</b>	2-[2-chloro-4-(methylsulfonyl)benzoyl]-1,3-cyclohexanedione	
<b>Mesotrione</b>	2-[4-(methyl sulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
<b>Tembotrione</b>	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoro ethoxy)methyl] benzoyl} cyclohexane-1,3-dione	

All compounds include a benzoyl core and in addition require at least two keto groups for the inhibitory activity. The structure-activity relationships of this chemical class were elucidated [5]. There is a rapid bleaching and quick elimination of the weeds when these herbicides are applied on the fields. A series of analogs of 1-Hydroxy-2-(alkylketo)-4,4,6,6-tetramethyl cyclohexen-3,5-diones were prepared by Ronald J Russay et al, at Stauffer Chemical's Western Research Center (WRC) in California in which the alkanoyl group was modified and a patent was obtained on this series of compounds [6]. These compounds had similar, weak herbicidal activity similar to that found with the lead compound (Leptospermone).

Recently, Hiroyuki Adachi synthesized novel bicyclo [4.1.0] heptane-2,4-dione derivatives and studied their herbicidal activity [7]. Some bicycle [4.1.0]heptanediones showed excellent herbicidal activity against weeds in a corn field.

Only a limited number of this class of triketone herbicides are known. Therefore the development of new triketone compounds which are efficient herbicides, are required in low quantities and are environmentally benign remains a challenge. The reported synthesis [4,8] of these compounds involves essentially the use of cyanide reagents which are hazardous and difficult to handle. The present synthesis uses simple harmless reagent like DMAP. The present study deals with the synthesis of new triketone compounds which are useful as herbicides. They are used in low concentrations to control the weeds.

*Parthenium hysterophorus* (family Asteraceae) commonly known as parthenium weed, congress grass, carrot weed or white top is a type of invasive plant species which is of major environmental threat to the natural and agro ecosystems in India and worldwide. According to a review by I. Gnanavel, the infestation of the weed causes yield losses upto 40% in several crops [9]. It has been achieved a status of the countries "Worst Weed" due to its allelopathic effects on agricultural crop production. 1% Glyphosate solution is found to be effective in controlling this weed in the seedling stage up to sufficient height with the onset of monsoon. But this application should be strictly made before blooming. Hence, in the present research, the weed chosen to study the herbicidal effects of the synthesized compounds is parthenium.

## Experimental

### *Materials and Reagents:*

The reagents and solvents used were of analytical grade and were used without further purification. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel GF254 plates using UV/Iodine as visualizing agent and Merk's silica gel (60-120 mesh) was used for column purification. Nuclear Magnetic resonance (NMR) spectra of the synthesized compounds were obtained using Varian Mercury plus spectrophotometer (USA) at 300 MHz using  $\text{CDCl}_3$  as a solvent and tetramethyl silane (TMS) as an internal standard. The chemical shifts are reported in ppm ( $\delta$  units) downfield from TMS. The coupling constants are reported in Hz. NMR spectra was recorded in SAIF-IIT Mumbai, Powai. Infrared spectra were recorded on FT-IR, Nicolet iS5 from Thermoscientific. The solid samples were prepared by using KBr pellets method and liquid samples by diluting with  $\text{CCl}_4$ . IR spectra were recorded in Research Department of Chemistry - B. N. Bandodkar college of Science, Thane. All the conversions and yields were rounded up to the nearest significant value.

### *Methods:*

The process for producing triketones involves the synthesis of the enol ester (3) from the acid chloride (2) and 1,3-cyclohexane dione. The final product (4) is obtained by rearrangement of the enol ester. This rearrangement reaction includes the use of strong cyanide reagents like sodium cyanide, potassium cyanide as well as acetone cyanohydrin. The use of these cyanide reagents are described as essential. The present study deals with the synthesis of triketone compounds without using the hazardous cyanide reagents. Simple reagent like Dimethyl amino pyridine (DMAP) is used to bring about the rearrangement of the enol ester to its triketone derivative.

Further to the efficient and successful synthesis of these 1,3-cyclohexane dione derivatives, their efficacy was studied on *Parthenium hysterophorous*, commonly known as Congress grass or Carrot weed.

## Synthesis: General Procedure

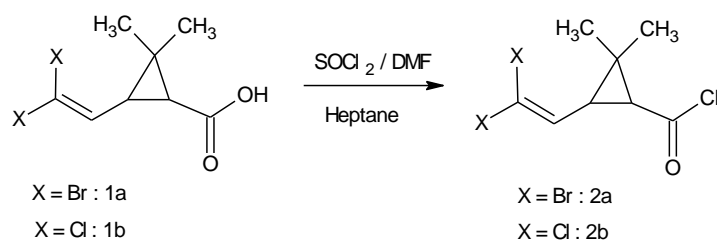
The general route for the synthesis of the substituted {2-[(2,2-dimethylcyclopropyl)- carbonyl] cyclohexane 1,3-dione} compounds is described here . All reactions were done in a three neck round bottom flask with magnetic stirrer bar, condenser and thermometer pocket in a heating water bath and a magnetic stirrer. The 3-substituted 2,2-dimethyl cyclopropyl carboxylic acid chlorides (**2**) (**Figure1**) were prepared by using the corresponding commercially available acids (**1**), thionyl chloride in heptane solvent and in the presence of catalytic amounts of DMF at 65-70°C.

**Compound 2a:** 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane-1- carbonyl chloride (**Figure1**)

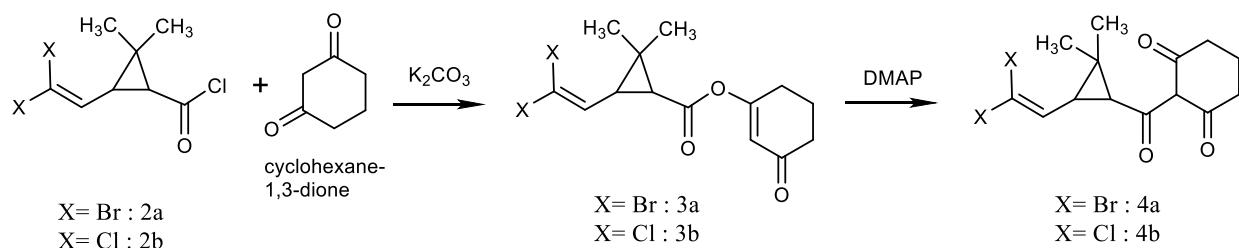
**Compound 2b:** 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1- carbonyl chloride (**Figure1**)

A slurry of **1** (0.01 moles), heptane (10 ml), thionyl chloride (2.2 ml) and 3-4 drops of DMF was heated to 60°C and maintained at this temperature for a period of 3 hours. During this time the reaction mass becomes a clear solution. The solvent was evaporated to give the crude acid chloride (**2**) which was then used for further reaction.

The enolates (**3**) were prepared by stirring 1,3-cyclohexane dione, potassium carbonate and acetonitrile solvent for a period of 2 to 3 hours at 25-30° C. The acid chloride was dissolved in acetonitrile and slowly added to the enolate slurry and stirred for 1 hour at 25-30°C. The enol ester could be isolated and recrystallized or the further reaction was done insitu by adding (DMAP) and heating the reaction mass to 50-70°C for a period of 7-8 hours. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was acidified with 2N HCl and extracted with dichloromethane. The extract was evaporated to give the triketone compound (**4b**) (**Figure2**). The isolated enol ester was dissolved in toluene and DMAP was added to it and maintained at 70°C for 7 hours. After reaction completion, the reaction mass was acidified with 2N HCl and extracted with dichloromethane. The extract was evaporated to give the crude triketone (**4a**) (**Figure2**). The crude compound was then recrystallized by using methanol. If necessary, the resulting crude product was purified by column chromatography using ethyl acetate and hexane.



**Figure 1** General synthetic route for the preparation of acid chlorides



**Figure 2** General synthetic route for the preparation of 1,3-cyclohexane dione derivatives

**Compound 3a:** 3-oxocyclohex-1-en-1-yl 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane-1-carboxylate (**Figure 2**)

A slurry of 1,3-cyclohexane dione (1.68 g), potassium carbonate (2.07 g) and acetonitrile (30 ml) was stirred for a period of 3 hours at 25-30° C. A solution of acid chloride **2a** (2.8 g) in acetonitrile (5 g) was slowly added to the above slurry over a few minutes and the reaction mass is stirred for 1 hour. The reaction progress was monitored by Thin Layer Chromatography (TLC) using hexane: ethyl acetate in the ratio (90:10). TLC indicated a single spot which was

different from the starting material. Therefore, the reaction mass was taken for workup. After this time, the reaction mass was acidified by adding 2N hydrochloric acid to it and the pH was adjusted to 2. The slurry was extracted with dichloromethane. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to get a sticky mass. This sticky mass was recrystallized from methanol to get white solids (**3a**) (2.25 g, 88%). Melting point: 96-97°C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.69 (d, 1H); δ 5.9 (t, 1H); δ 2.55 (t, 2H); δ 2.4 (t, 2H); δ 2.09 (m, 2H); δ 2.07 (t, 2H); δ 1.97 (d, 1H); δ 1.31 (s, 3H); δ 1.29 (s, 3H)  
IR: 1720, 1675, 1642, 1110, 1072cm<sup>-1</sup>.

**Compound 4a:** 2-[[3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropyl]carbonyl]cyclohexane-1,3-dione (**Figure2**)

Compound **3a** (0.4 g), toluene (10 ml) and Dimethyl amino pyridine (DMAP, 0.08 g) were stirred at 70°C for a period of 7 hours. Water was added to the reaction mass and the layers were separated. The toluene layer was washed with brine and concentrated to get off white solids (**4a**) (0.35 g) in 87.5% yield. TLC indicated a single spot which was different from the starting material and hence the product was not subjected to column chromatography. Melting point: 91-92°C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 18.05 (s, 1H), δ 6.86 (d, 1H); δ 2.66 (t, 2H); δ 2.5 (td, 2H); δ 2.17 (t, 2H); δ 1.97 (d, 1H); δ 1.38 (s, 3H); δ 1.23 (s, 3H)  
IR: 1661, 1560, 1114, 1071, 594cm<sup>-1</sup>

**Compound 4b:** 2-[[3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropyl]carbonyl]cyclohexane-1,3-dione (**Figure2**)

A slurry of 1,3-cyclohexane dione (1.68 g), potassium carbonate (2.07 g) and acetonitrile (30 ml) were stirred for a period of 2 and a half hours at 25°C. A solution of compound **2b** (2.8 g) in acetonitrile (5 g) was slowly added to the above slurry over a few minutes and the reaction mass was stirred for 1 hour. The reaction progress was monitored by TLC. It showed the formation of enol-ester intermediate (Compound **3b**). After 1 hour, Dimethyl amino pyridine (DMAP, 0.75 g) was added to the reaction mass and heated at 50°C and maintained for a period of 8 hours. The reaction progress was monitored by TLC. After the reaction was complete, the reaction mass was acidified by adding 2N hydrochloric acid to it and the pH was adjusted to 2. The reaction mass was extracted with dichloromethane. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to get a sticky mass. The product was purified by using column chromatography to give white solids (**4b**) (3.2 g) in 87.5% yield. Melting point: 51-52°C.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 18.2 (s, 1H), δ 6.33 (d, 1H); δ 5.66 (dd, 1H); δ 3.65 (d, 1H); δ 2.60 (m, 2H); δ 2.26 (m, 2H); δ 2.05 (m, 2H); δ 1.97 (s, 3H); δ 1.27 (s, 3H).  
IR: 1661, 1561, 1110, 1045cm<sup>-1</sup>

### Herbicidal Activity

A herbicidal formulation was prepared by using equimolar quantities of Compound **4a** and Compound **4b** along with 50% choline chloride solution to form an aqueous concentrate formulation. The aqueous concentrate formulation thus prepared was diluted with water to a 0.5% concentration and was used.

#### (i) Pre-emergence herbicidal action (inhibition of germination).

Seeds of Congress grass weed (*Parthenium hysterophorous*) and green chilli (*Capsicum frutescens*, crop plant) were planted in plastic pots (500cm<sup>3</sup>). Immediately after sowing the seeds, the surface of the soil was sprayed with the aqueous solution (0.5%) of the aqueous concentrate formulation as prepared above. The pots were kept at 24-26°C with 50-60% humidity, and watered regularly. The test results were evaluated after three weeks on a scale of zero (no damage to weeds or crops) and 100 (complete killing of weeds or crops).

(ii) **Post emergence herbicidal action (contact herbicide).** Congress grass (*Parthenium hysterophorous*) weed plants and green chilli (*Capsicum frutescens*, crop plant) plants were grown in plastic pots (500cm<sup>3</sup>) and after emergence (in

the 4- to 6-leaf stage) the plants are sprayed with aqueous solution (0.5%) of the aqueous concentrate formulation as prepared above. The treated plants were kept at 24-26 °C with 50-60% humidity. The test was re-evaluated after two weeks after the treatment.

## Results and Discussion

**Synthesis:** To summarize, novel triketone herbicidal compounds were prepared in good yields by a simple and practical process and their efficacy was studied. The rearrangement of the enol esters (3a and 3b) to their corresponding triketone derivatives (4a and 4b) was done easily using DMAP as a catalyst. This is a very convenient and simple process without involving hazardous cyanide reagents such as sodium cyanide, potassium cyanide and acetone cyanohydrin which are reported [4,8].

**Herbicidal activity:** Herbicidal activities of synthesized triketone derivatives against Congress grass weed were evaluated and the results are reported in Table 2.

**Table 2** Herbicidal activity and crop safety of {2-[(2,2-dimethylcyclopropyl)-carbonyl] cyclohexane-1,3-dione derivatives

Compound no.	Pre emergence control	Post emergence control	<i>Capsicum frutescens</i>
4a	100	100	0
4b	100	100	0
Control (no compound)	0	0	0
Glyphosate	100	100	0

The initial investigation of the herbicidal activity of the {2-[(2,2-dimethylcyclopropyl)-carbonyl] cyclohexane-1,3-dione derivatives shows comparable herbicidal activity with respect to the known herbicide Glyphosate. The degree of injury or control was determined by comparison with untreated plants. There is zero damage observed in the crop plant (green chilli), which means that it shows tolerance towards these compounds, while compounds 4a and 4b showed 100% herbicidal activity on the weeds.

Further application of these herbicides on other grass weeds is in progress.

## References

- [1] Istavan Jablonkai (2011), Molecular Mechanism of Action of Herbicides, Herbicides-Mechanisms and Mode of Action, Dr. Mohammed Nagib Hasaneen (Ed.), ISBN:978-953-307-744-4, InTech, 22nd December 2011.
- [2] Mitchell G, Bartlett DW, Fraser TEM, Hawkes TR, Holt DC, Townson JK, Wichert RA.; Mesotrione: a new selective herbicide for use in maize. Pest Management Science. 2001; 57:120-128.
- [3] Beaudegnies R, Edmunds AJF, Fraser TEM, Hall RG, Hawkes TR, Mitchell G, Schaetzer J, Wendeborn S, Wibley J. Herbicidal 4-hydroxyphenylpyruvate dioxygenase inhibitors – A review of the triketone chemistry story from a Syngenta perspective. Bioorganic & Medicinal Chemistry. 2009; 17:4134-4152.
- [4] Michaely, W.J., Kratz, G.W., Certain 2-(2-substituted benzoyl)-1,3- cyclohexanediones and their use as herbicides, US 4,780,127 (1988).
- [5] David L. Lee, Christopher G. K, William J. M, Hsiao-Ling Chin, Nhan H. Nguyen, Charles G. Carter, Thomas H. Cromartie, Byron H. Lake, John M. Shribbs, Torquil Fraser; Pest Management Science; Pesticide Science; Issue: Current research at Zeneca Agrochemicals; Volume 54, Issue 4, pages 377–384, December 1998.
- [6] Reed A. Gray, Chien K. Tseng, Ronald J. Rusay, 1-Hydroxy-2-(alkylketo)-4,4,6,6-tetramethyl cyclohexen-3,5-diones, US4,202,840(1980).

- [7] Hiroyuki ADACHI, Akiyoshi UEDA, Toshio AIHARA, Kazuyuki TOMIDA, Takashi KAWANA and Hideo HOSAKA, Synthesis of new bicyclo[4.1.0]heptane-2,4-dione derivatives and their herbicidal activity, *J. Pestic. Sci.*, 32(2), 112–119 (2007), DOI: 10.1584/jpestics.G06-30.
- [8] Heather James B., Milano Pamela D., Process for the production of acylated 1,3-dicarbonyl compounds, US 4695673
- [9] I. Gnanavel; *Parthenium hysterophorus* L.: A Major Threat to Natural and Agro Eco-systems in India; Review article; *Science International*; DOI: 10.5567/sciintl.2013.186.193.

© 2015, by the Authors. The articles published from this journal are distributed to the public under “**Creative Commons Attribution License**” (<http://creativecommons.org/licenses/by/3.0/>). Therefore, upon proper citation of the original work, all the articles can be used without any restriction or can be distributed in any medium in any form.

**Publication History**

Received 29<sup>th</sup> July 2015  
Revised 17<sup>th</sup> Aug 2015  
Accepted 11<sup>th</sup> Sep 2015  
Online 30<sup>th</sup> Sep 2015