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A new and efficient route for 1,3,3′-triketones

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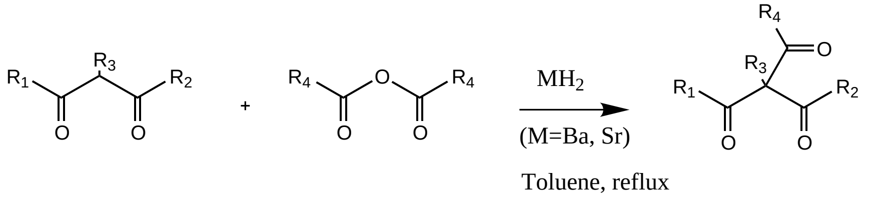
Abstract—Cyclic and acyclic 1,3,3′-triketones were prepared by the reactions adopting β-diketones and anhydrides in the presence of barium or strontium hydrides in high yields. Crystal structure of 4-acetyl-2,2,6,6-tetramethyl-3,5-heptanedione (**3a**) represented the dorminant keto form and provided evidence for intermolecular C–H···O hydrogen bonds (average C···O distance; 3.437 Å, average C–H···O angle; 169.25°). © 2001 Elsevier Science Ltd. All rights reserved.

1,3,3′-Triketones, first prepared by reactions between β-diketones and acid anhydrides in the presence of carboxylate anions in as early as 1955,[1] have attracted interest due to application of active herbicides in which 1,3,3′-triketone derivatives inhibit *p*-hydroxyphenylpyruvate dioxygenase (HPPD).[2] Zeneca Agrochemicals first reported that herbicidal 2-benzoyl-1,3-cyclohexanediones, referred to as the triketones, effectively inhibit the action of HPPD in 1982.[3] Since then, most major agrochemical companies are reported to have or have had research projects in this area. Another pharmaceutical activity of these compounds in the treatment of tyrosinaemia, a disorder involving increased concentrations of tyrosine in the blood, was found.[4]

Also, keto-enol tautomerism in these compounds has been extensively studied by novel methods such as the deuterium isotope effect.[5] Recently, multidentate ligands have attracted much interest due to enhanced stability and possible formation of multinuclear complexes. Tetraketones and Schiff bases have been utilized to take advantage of these properties.[6] When we consider the rich chemistry of β-diketonates[7] and 1,3,5-



1a R_1, R_2 = t-Bu, R_3=H	**2a** R_4 = Me	**3a** R_1, R_2 = t-Bu, R_3=H, R_4= Me
1b R_1, R_2 = t-Bu, R_3=H	**2b** R_4 = t-Bu	**3b** R_1, R_2 = t-Bu, R_3=H, R_4 =t-Bu
1c R_1, R_2 = -$(CH_2)_2$-, R_3=H	**2a** R_4 = Me	**3c** R_1, R_2 = -$(CH_2)_2$-, R_3=H, R_4 =Me
1d R_1, R_2 = -$(CH_2)_3$-, R_3=H	**2a** R_4 = Me	**3d** R_1, R_2 = -$(CH_2)_3$-, R_3=H, R_4 = Me
1e R_1, R_3 = -$(CH_2)_3$-, R_2=Me	**2a** R_4 = Me	**3e** R_1, R_3 = -$(CH_2)_3$-, R_2, R_4 = Me
1f R_1, R_3 = -$(CH_2)_4$-, R_2=Me	**2a** R_4 =Me	**3f** R_1, R_3 = -$(CH_2)_4$-, R_2, R_4 =Me

Scheme 1.

Keywords: 1,3,3′-triketones; β-diketones; anhydrides; barium (strontium) β-diketonates; intermolecular C–H···O hydrogen bonds.

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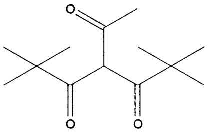
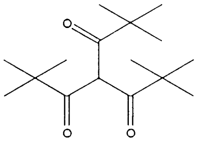
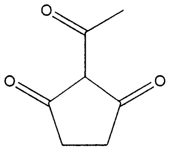
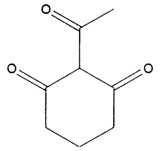
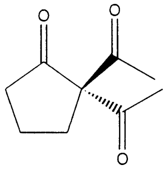
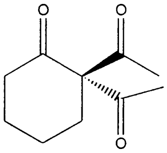
triketonates,[8] 1,3,3′-triketones can be used as possible tridentate ligands commanding facial geometry and new class of chemistry can be examined.

Several preparative methods have been adopted. Conventional acylation of β-dicarbonyl compounds aided by bases suffers low yields due to undesired products resulting from *O*-acylation and other side reactions. Taylor et al. claimed that treatment of thallous salts of β-dicarbonyl compounds, formed by the reaction between thallium ethoxide and β-dicarbonyl compounds, with acyl fluorides produced 1,3,3′-triketones in high yields even though only one example was reported.[9] However, treatment of thallous salts of β-dicarbonyl compounds with other acyl halides produced *O*-acylated products. Improved synthesis of 2-benzoylcyclohexane-1,3-dione derivatives was reported by the reaction of cyclohexane-1,3-diones with benzoylcyanide.[3] However, no general preparative methods for cyclic or acyclic 1,3,3′-triketones have been reported.

In this paper, a new and efficient pathway for 1,3,3′-triketones will be addressed. This method can be applicable to the synthesis of both cyclic and acyclic 1,3,3′-triketones with even bulky substituents such as *t*-butyl group and high yield is another advantage.

As shown in Scheme 1, various types of β-diketones reacted with anhydrides in the presence of BaH$_2$ or SrH$_2$ (0.5 equivalent) to produce 1,3,3′-triketones with metal acetates almost quantitatively except acetylcycloalkanone cases.[10] Table 1 summarizes the reaction

Table 1. Summary of reaction conditions and results

Entry	**Product**	**Metal Compound**	Reaction medium and condition (rf : refluxed rt : room temp.)	**Reaction time**	Uncharacterized Side Product (USP) or Starting Material (SM)	Yield (%) (P : Purified, CP ; Crude Product)
3a		BaH$_2$ SrH$_2$ Ba(tmhd)$_2$ Sr(tmhd)$_2$ NaH	Toluene (rf) THF (rf) Toluene (rf) Toluene (rt) Toluene (rt) THF (rf)	8hr 15hr 8hr 1hr 1hr 24hr	no no no no no no	96 (P) 92 (P) 95 (P) 93 (P) 91 (P) 89 (P)
3b		BaH$_2$ SrH$_2$ Ba(tmhd)$_2$	Toluene (rf) Toluene (rf) Toluene (rt)	8hr 8hr 1hr	no no no	79 (P) 94 (P) 90 (P)
3c		BaH$_2$ SrH$_2$	Toluene (rf) THF (rf) Toluene (rf)	8hr 6hr 8hr	USP 3 over (no SM) no USP 3 over (no SM)	Failed 89 (P) Failed
3d		BaH$_2$ SrH$_2$	Toluene (rf) THF (rf) Toluene (rf)	7hr 4hr 8hr	USP 4 over (no SM) no USP 4 over (no SM)	Failed 93 (P) Failed
3e		BaH$_2$ SrH$_2$	Toluene (rf) THF (rf) Toluene (rf)	8hr 32hr 8hr	SM SM SM	50 (CP) 31 (P) 50 (CP)
3f		BaH$_2$ SrH$_2$	Toluene (rf) THF (rf) Toluene (rf)	8hr 32hr 8hr	SM SM SM	60 (CP) 44 (P) 60 (CP)

conditions and product data. A typical triketone was crystallographically characterized and shown in Fig. 1. However, reaction with acetylacetone (acac) cannot avoid side reactions (eight spots in TLC) possibly due to the presence of several α protons next to the car-bonyl groups. It was observed that the reaction rates increased in the order of acetylcycloalkanone, cyclo-β-diketones, and alkyl-β-diketones. In the case of cyclo-β-diketones, selectivity towards 1,3,3′-triketones was found to be dependent on the solvents. In toluene, crude products resulted in three or four spots in TLC, while 1,3,3′-triketones were the only isolated organic product in THF. It appears that higher reaction temperatures in refluxing toluene may induce further reaction such as decomposition, but other organic compounds could not be characterized due to failure in isolation. However, it cannot be completely excluded that the solubility of β-diketones or polarity of solvents may be the reasons for these different behaviors. Also, it was observed that cyclohexa-β-dione made the reaction proceed faster than cyclopenta-β-dione.

Barium (or strontium) β-diketonates appear to be intermediates because adoption of Ba(tmhd)$_2$ (tmhd = 2,2,6,6-tetramethyl-3,5-heptanedione) instead of BaH$_2$ and tmhd causes the reaction to proceed to completion within 1 h even in room temperature. However, no reaction proceeded with Ba(tmhd)$_2$ hydrates.

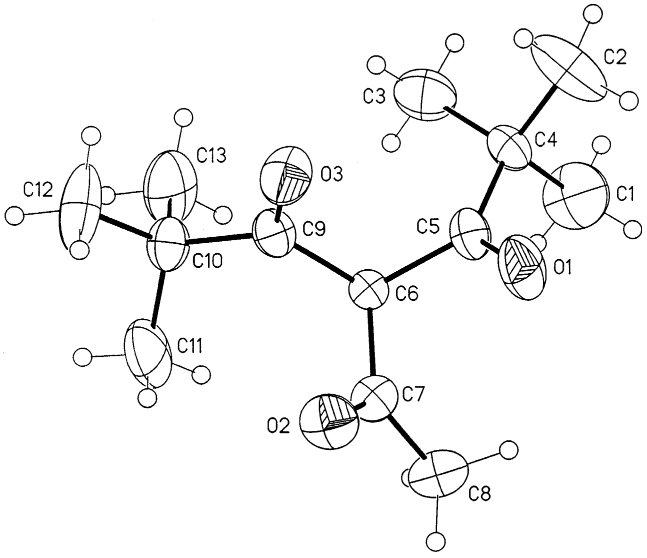


Figure 1. 20% thermal ellipsoid diagram for the X-ray crystallographic geometry of 4-acetyl-2,2,6,6-tetramethyl-3,5-heptanedione. Selected bond lengths (Å) and angles (°): C6–C5, 1.529(4); C6–C7, 1.513(4); C6–C9, 1.523(4); C5–O1, 1.219(4); C7–O2, 1.222(4); C9–O3, 1.207(3), C5–C6–C7, 107.1(2); C5–C6–C9, 110.6(2); C7–C6–C9, 110.5(2).

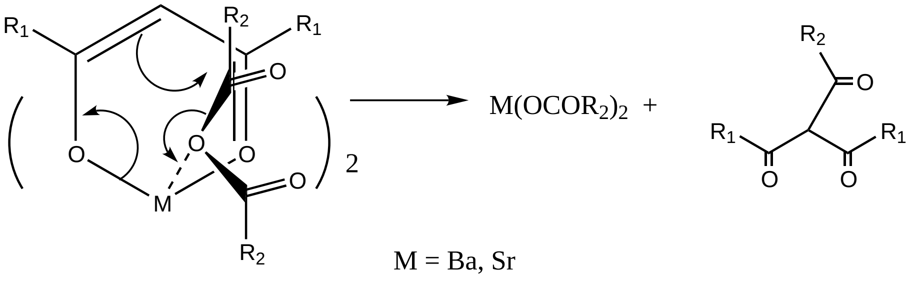
On the other hand, Ba(NO$_3$)$_2$ with NEt$_3$, Ba(O*i*-Pr)$_2$, and Sr(acetate)$_2$ failed to make the reaction proceed. Cyclic anhydrides such as succinic anhydride and glutaric anhydride and diimides also failed to produce corresponding triketones.

From these results, a plausible pathway is proposed, as shown in Scheme 2.

Much faster reaction rates with anhydrous Ba(tmhd)$_2$ strongly supports the metal β-diketonate intermediate and that the formation of metal β-diketonates is the rate determining step. The proposed pathway is a kind of replacement reaction as reported in the reactions of metal β-diketonates with acyl halides,[11] where similar intermediates were proposed. Nucleophilic attack of coordinated β-diketonates onto anhydrides is another possibility as reported in the interaction of β-diketonates with diene complexes of Pd(II) and Pt(II).[12] No reaction with Ba(tmhd)$_2$ hydrates effectively excluded this possibility. Coordinated H$_2$O prevented anhydrides from coordination and joining the reaction. Also, no reactions adopting other barium or strontium compounds where other coordinating ligands are present support this proposition.

Since the predominant interatomic interactions in Group II β-diketonate complexes are electrostatic (i.e. ionic) in nature and the average coordination numbers observed for Sr and Ba complexes are 6–8,[7b] Lewis bases such as anhydrides are expected to fill the coordination sites. An ethereal oxygen atom coordinates over a carbonyl one because many examples with coordinated ethers are reported, while complexes with coordinated ketones are rare.[11] Also, model analysis shows coordination through carbonyls places the substituents in a position to block the nucleophilic attack of β-diketonates onto the carbonyl group. In the same manner, inertness of cyclic anhydrides towards nucleophilic attack can be explained. In the cases of diimides, the presence of hydrogen on a nitrogen atom may retard the coordination, which results in no reaction.

Adoption of cyclo-β-diketones requires the deviation from planar nature of coordinated β-diketonates, which retards the nucleophilic attack. The larger ring of cyclohexane-1,3-dione in comparison to cyclopentane-1,3-dione induces less deviation of planarity, which results in a faster reaction rate. In the case of acetylcycloalka-



Scheme 2.

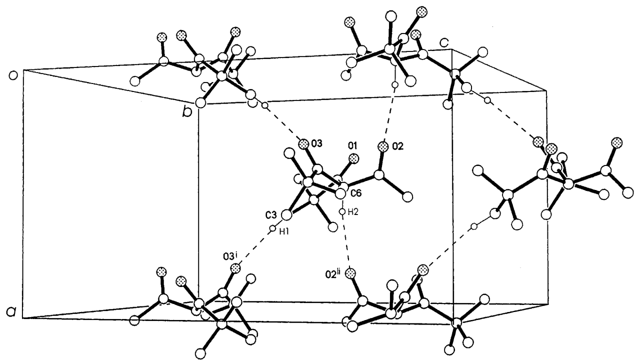


Figure 2. Packing structure of the molecules of 4-acetyl-2,2,6,6-tetramethyl-3,5-heptanedione stabilized by C–H···O hydrogen bonds. Non-hydrogen bonding H atoms are omitted for clarity.

none, the slowest reaction rate appears to originate from the fact that formation of enol and coordination to a metal are effectively suppressed because methines of β-diketonates locate on the bridge-head of the ring.

NaH also produced triketones but at a much slower rate. In the preparation of triketones with alkyl substituents, it took at least 3 or 4 days to complete the reaction even in refluxing toluene. This may result from the fact that Na is smaller than Sr and Ba and simultaneous coordination of both β-diketonates and anhydrides is not easy. Actually, sodium β-diketonates are reported to have a 4–6 coordination number, which is less than Sr and Ba analogues.

The presence of acid such as formic acid makes the triketone decompose to the corresponding β-diketones. Bubbling H_2 into the reaction mixture induced no reaction, possibly due to blocking the coordination of anhydrides by preoccupying the coordination sites around metal ions.

The crystal structure shown in Fig. 1 represented the dominant keto form, as evidenced in the ^{1}H NMR spectrum where the methine peaks appears at 5.63 ppm, which is quite unusual. 2-Acyl-1,3-cycloalkanediones[13] are only observed in the enolic form, whereas triacetylmethane[14] is reported to exist in both the enolic and keto forms. Three carbonyl groups are located in *syn* manner, which will address facial conformation if this is coordinated to an appropriate metal ion. In Fig. 2, intermolecular hydrogen bonds in this crystalline compound were illustrated. Although H atoms have been included in their idealized positions, some methyl H atoms of *t*-butyl groups are located close to the carbonyl O atoms of the neighboring molecules, providing evidence for intermolecular C–H···O hydrogen bonds (average C···O distance; 3.437 Å, average C–H···O angle; 169.25°).[15]

Further studies to clarify the reaction mechanism and to prepare the new metal complexes with facial geometry are in progress.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 163331. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44(0)1223-3336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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References

1. Rogers, N. A. J.; Smith, H. *J. Chem. Soc.* **1955**, 341.
2. Lee, D. L.; Knudsen, C. G.; Michaely, W. J.; Chin, H.-L.; Nguyen, N. H.; Carter, C. G.; Cromartie, T. H.; Lake, B. H.; Shribbs, J. M.; Fraser, T. *Pestic. Sci.* **1998**, *54*, 377 and references cited therein.
3. Michaely, W. J.; Kratz, G. W. EP 0135191, 1986.
4. Ellis, M. K.; Lindestedt, S. T.; Lock, E. A.; Markstedt, M. E. H.; Mutter, L. C.; Prisbylla, M. P. WO 93/00080, 1992.
5. Bolvig, S.; Duus, F.; Hansen, P. E. *Magn. Reson. Chem.* **1998**, *36*, 315.
6. (a) Garnovskii, A. D.; Nivorozhkin, A. L.; Minkin, V. I. *Coord. Chem. Rev.* **1993**, *126*, 1; (b) Fenton, D. E.; Regan, C. M. *Inorg. Chim. Acta* **1982**, *58*, 83; (c) Fenton, D. E.; Tate, J. R.; Casellato, U.; Tamburini, S.; Vigato, P. A.; Vidali, M. *Inorg. Chem. Acta* **1984**, *83*, 23; (d) Lintvedt, R. L.; Schoenfelner, B. A.; Ceccarelli, C.; Glick, M. D. *Inorg. Chem.* **1982**, *21*, 2114.
7. (a) Metrotra, R. C.; Bohra, R.; Gaur, D. P. *Metal β-Diketonates and Allied Derivatives*; Academic Press: London, UK, 1978; (b) Otway, D. J.; Rees, Jr., W. S. *Coord. Chem. Rev.* **2000**, *210*, 279; (c) Nikonov, M. V.; Chizhov, D. L.; Ratner, V. G.; Pashkevich, K. I. *J. Fluorine Chem.* **2000**, *106*, 115.
8. (a) Harada, Y.; Mizobe, Y.; Hidai, M. *J. Organomet. Chem.* **1999**, *574*, 24; (b) El-Qisairi, A.; Henry, P. M. *J. Organomet. Chem.* **2000**, *603*, 50; (c) Arimoto, H.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 4581.
9. Taylor, E. C.; Alexander, M. US Patent 3,947,488, 1974.
10. Detailed reaction procedures and spectroscopic data including crystallographic data can be found in the supporting information sheet.
    A representative experimental procedure is as follows. A solution containing 2.95 g (15.71 mmol) of 2,2,6,6-tetramethyl-3,5-heptanedione (tmhd) in toluene (20 ml) was added to a suspended solution of BaH_2 (1.0 g, 7.14 mmol) in toluene (15 ml). After stirring for 10 min at room temperature, a solution of acetic anhydride (1.46 g, 14.28 mmol) in toluene (10 ml) was added to the mixture. The reaction mixture was refluxed for 8 h and then was cooled down to room temperature. The resulted solution was filtered to remove insoluble barium acetate and the

filtrate was evaporated under reduced pressure. The residue was recrystallized in hexane (20 ml) at −20°C to obtain a colorless crystal (3.10 g, 95.98%). **^{1}H NMR** (199.976 MHz, $\mathrm{CDCl_3}$): 5.63 (s, 1H, $\mathrm{((CH_3)_3CC(O))_2C}\mathit{H}\mathrm{(C(O)CH_3)}$), 2.21 (s, 3H, $\mathrm{((CH_3)_3CC(O))_2CH(C(O)C}\mathit{H}_3\mathrm{)}$), 1.16 (s, 18H, $\mathrm{((C}\mathit{H}_3\mathrm{)_3CC(O))_2CH(C(O)CH_3)}$; **^{13}C NMR** (50.289 MHz, $\mathrm{CDCl_3}$): 203.11 (s, $\mathrm{((CH_3)_3C}\mathit{C}\mathrm{(O))_2CH(C(O)CH_3)}$), 197.12 (s, $\mathrm{((CH_3)_3CC(O))_2CH(}\mathit{C}\mathrm{(O)CH_3)}$), 68.96 (s, $\mathrm{((CH_3)_3CC(O))_2}\mathit{C}\mathrm{H(C(O)CH_3)}$), 44.11 (s, $\mathrm{((CH_3)_3}\mathit{C}\mathrm{C(O))_2CH(C(O)CH_3)}$), 27.34 (s, $\mathrm{((CH_3)_3CC(O))_2CH(C(O)}\mathit{C}\mathrm{H_3)}$), 24.93 (s, $\mathrm{((}\mathit{C}\mathrm{H_3)_3CC(O))_2CH(C(O)CH_3)}$; anal. calcd for $\mathrm{C_{13}H_{22}O_3}$: C, 68.99; H, 9.80; found: C, 68.57; H, 10.23.

11. (a) Barry, W. J. *J. Chem. Soc.* **1960**, 670; (b) Murdoch, H. D.; Nonhebel, D. C. *J. Chem. Soc.* **1962**, 2153; (c) Nonhebel, D. C. *J. Chem. Soc.* **1962**, 4628; (d) Nojiri, T.; Motoi, M.; Hashimoto, I. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 850.
12. Johnson, B. F. G.; Lewis, J.; Subramaniam, M. S. *J. Chem. Soc. (C)* **1968**, 1993.
13. (a) Liepins, E.; Petrova, M. V.; Gudrimiece, E.; Paulins, I. *Magn. Reson. Chem.* **1989**, *27*, 907; (b) Forsen, S.; Merenyi, F.; Nilsson, M. *Acta Chem. Scand.* **1964**, *18*, 1208.
14. (a) Dreyfus, M.; Garnier, F. *Tetrahedron* **1974**, *30*, 133; (b) Yoshida, Z.; Ogoshi, H.; Tokumitsu, T. *Tetrahedron* **1970**, *26*, 5691.
15. (a) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063; (b) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290.