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Metal- and Base-Free Combinatorial Reaction for C-Acylation of 1,3-Diketo Compounds in Vegetable Oil: The Effect of Natural Oil

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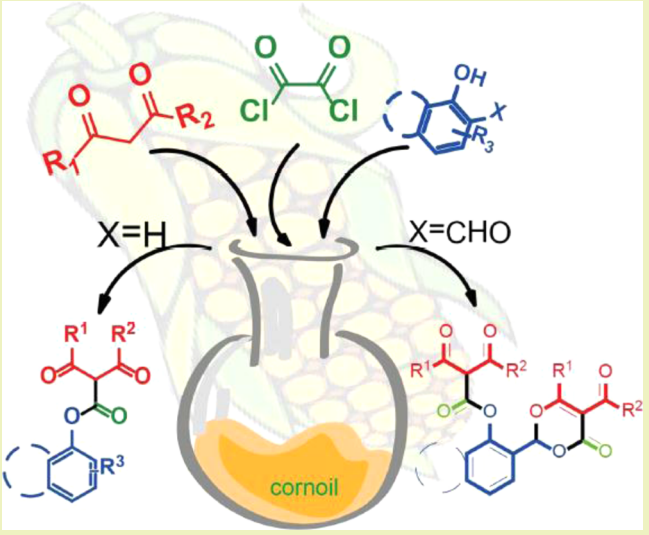
Supporting Information

ABSTRACT: C-acylation of 1,3-diketo compounds has been done successfully employing 1,3 diketo compounds, oxalyl chloride, and phenol derivatives through metal, base, and toxic solvent-free protocol. Dioxinone ring-bearing 1,3,3′ tricarbonyl moiety was also obtained in the same conditions using salicyl aldehyde. All reactions were carried out in vegetable oil.



KEYWORDS: *Tricarbonyl derivatives, Corn oil, Dioxinone, Green chemistry, X-ray*

INTRODUCTION

C-acylation of 1,3-diketo compounds to obtain 1,3,3′-tricarbonyl compounds has been performed by reactions between 1,3-diketo compounds and acid anhydrides in the presence of a base as early as 1955.[1] Since then, these compounds have attracted attention because 1,3,3′ tricarbonyl derivatives inhibit *p*-hydroxyphenylpyruvate dioxygenase, which is an important enzyme for herbicide research.[2] Moreover, tricarbonyl compounds are a vital intermediate for synthesis of pharmaceutically important compounds, e.g., Rimonabant and 5-deazaaminopterin.[3−6] Furthermore, these compounds have been employed for liquid crystal researches.[7] Surprisingly, although there are many applications of these tricarbonyl compounds, only a limited number of procedures have been reported. Unfortunately, those methods usually require use of stoichiometric amounts of strong bases such as BaH_2,[8] EtMgBr,[9] and n-BuLi.[10] These bases are not suitable for sensitive substrates and cannot be disposed of easily. Notably, Zhou et al. developed a method for C-acylation of 1,3-diketo compounds by using catalytic amount of $SmCl_3$ in toluene.[11] Rathke and Cowen reported also a $MgCl_2$-promoted C-acylation of 1,3-diketo compounds in acetonitrile and tertiary amine or pyridine.[12] The strategies in order to develop clean technologies for chemical processes target a balance between the economy and environmental aspects. In this context, a metal-free, base-free, and toxic solvent-free method for C-acylation of 1,3-diketo compounds remains a challenge. Despite the fact that Munshi and Beckman have developed a new process for obtaining *β*-ketoesters appling a reversible CO_2 carrier (RCC), this method has involved the use of strong bases like n-BuLi and DBU.[13] In all previously mentioned processes, base, metal, and toxic solvents have been used. With this in mind, we envisioned obtaining a green and atomically economic method for C-acylation of 1,3-diketo compounds. Herein, we wish to report a highly efficient green method for C-acylation of 1,3-diketo compounds in vegetable oil without using a metal and base (Scheme 1).

Vegetable oils are a key class of renewable raw materials and base stock for new green chemistry. The biodegradability of vegetable oils is better than that of mineral oils, polyalphaolefins, or polyalkylene glycols.[14] Also, they are nontoxic and nonvolatile and have a high shear stability, high flash point, and

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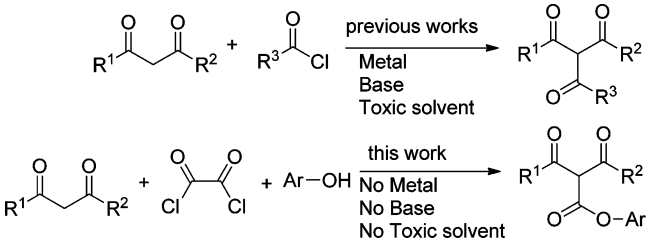
Scheme 1. Acylation of 1,3-Diketo Compounds

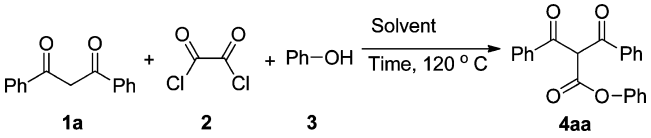


high viscosity index.[14] To the best of our knowledge, this is the first time for using vegetable oil for synthetic chemistry.

RESULTS AND DISCUSSION

As a model reaction, dibenzoylmethane (**1a**), oxalyl chloride (**2**), and phenol (**3a**) were employed. For this reaction, a variety of vegetable oils and toxic solvents at different temperature were examined. The optimized reaction conditions for each solvent are reported in Table 1.

Table 1. Optimization of Reaction Conditions for C-Acylation of 1,3-Diketo Compounds[a]



1a **2** **3** **4aa**

entry	solvent	temp (°C)	time	yield (%)[b]
1	nuts oil	120	15 min	89
2	olive oil	120	15 min	91
3	corn oil	120	15 min	95
4	corn oil	120	1 h	91
5	flower oil	120	15 min	91
6	–	120	2 h	41[c]
7	xylene	120	24 h	–[d]

[a]Reaction Condition: (1.0 mmol) 1,3-diketo compound (**1a**), (1.0 mmol) oxalyl chloride (**2**), (1.0 mmol) phenol (**3a**), solvent (1 mL). [b]Crude yield. [c]The reaction was carried out absence of the solvent. [d]Desired product was observed in a very small amount based on ^{1}H NMR

As seen in Table 1, the best results were obtained in corn oil[15] at 120 °C for 15 min. (Table 1, entry 3), and in this time, the product precipitated. The vegetable oils showed selectivity for acylation despite of the fact that some cyclic additional products might be formed.[16] Furthermore, it decreased the reaction time. This may be due to the fact that the triglyceride unit and long alkyl chain of oils take place a cage for the reaction that allow acylation of the product, but it is not clear why this cage leads to just acylation of the product. To prove this point, the same reaction was carried out in the absence of the oil (Table 1, entry 6). This reaction gave the acylation product but in a lower yield than the reaction in oil, and there are also some unidentified products that might be side products judged by the ^{1}H NMR spectrum. Furthermore, it was detected that starting materials were not totally consumed in 2 h. On the other hand, when the reactions run in such a toxic solvent as xylene for 24 h (Table 1, entry 7), the desired product occurred in the result of long reaction times and very low yields with some unidentified products (Figure 1).

All of these results come from the effect of oil on the desired compounds. Another important point of this research is that after obtaining **4aa**, the vegetable oil was recovered. After finishing the reaction to get **4aa**, 2 mL of hexanes was added to the reaction mixture. The precipitated product was filtered off, and hexanes were collected. To get used oil, hexanes were evaporated by vacuum. Every vegetable oil was independently used three times for the same reaction to screen its reactivity. According to the outcomes, we have determined that the recovered natural oils retain their reactivity in terms of yield (Table 2). There are two possibilities to decrease the reactivity of the vegetable oil. One of them is the reaction between corn oil and oxalyl chloride. To eliminate this possibility, we have heated corn oil with oxalyl chloride for 1 h. We have realized that there is no change in the oil based on the ^{1}H NMR. Another possibility is that every running reaction leaves 2 mol of HCl in the vegetable oil. We assume that this HCl affects the reactivity of the vegetable oil, and the reactivity of the used oil is decreasing because of the increasing amount of HCl after further runs.

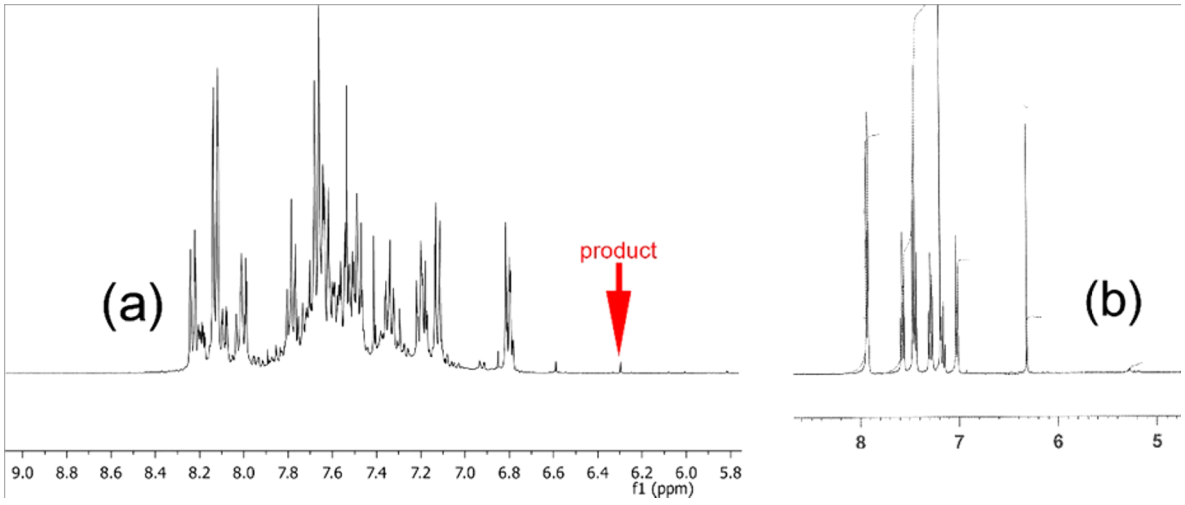


Figure 1. (a) ^{1}H NMR spectrum of the reaction in xylene for 24 h for **4aa** (crude NMR). (b) ^{1}H NMR spectrum for the reaction in corn oil for 15 min for **4aa** (crude NMR).

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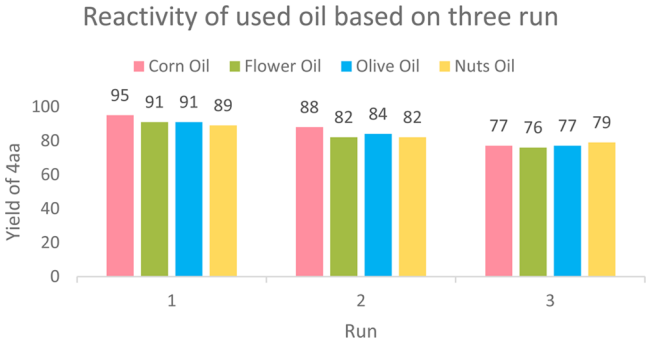
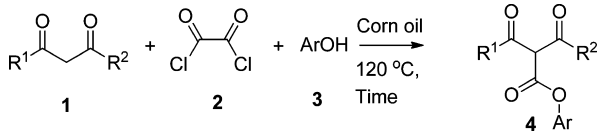
Table 2. Reactivity of Used Oil Based on Three Runs



With the optimized reaction conditions in hand, the generality for C-acylation of 1,3-diketo compounds was examined (Table 3).

Table 3. Generality for C-Acylation of 1,3-Diketo Compounds[a]

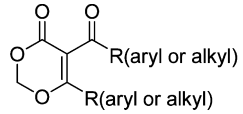


entry	R^1	R^2	Ar	time	yield (%)[b]
1	Ph	Ph	Ph	15 min	95 (**4aa**)
2	Ph	Ph	2-naphtyl	1 h	95 (**4ab**)
3	Ph	Ph	1-naphtyl	1.5 h	89 (**4ac**)
4	Ph	Ph	*p*-Cl-Ph	1.5 h	85 (**4ad**)
5	*p*-OMe-Ph	*p*-t-Bu-Ph	Ph	30 min	88 (**4ba**)
6	*p*-OMe-Ph	*p*-t-Bu-Ph	2-naphtyl	40 min	86 (**4bb**)
7	*p*-OMe-Ph	*p*-t-Bu-Ph	1-naphtyl	1 h	87 (**4bc**)
8	*p*-OMe-Ph	*p*-t-Bu-Ph	*p*-Cl-Ph	1.5 h	90 (**4bd**)

[a]Reaction conditions are presented. [b]Crude yield.

The optimized reaction conditions were employed to react with some phenol and 1,3-diketo derivatives. It was found that the reactions between substituted, unsubstituted, or benzene analogues of phenol derivatives and 1,3-diketo compounds in the presence of oxalyl chloride gave expected products.[17] Moreover, instead of phenol, the reaction of hydroquinone and 1,3-diketones gave a bulky and symmetric type of tricarbonyl derivatives (**4ae** and **4be**) in high yield (Scheme 2).

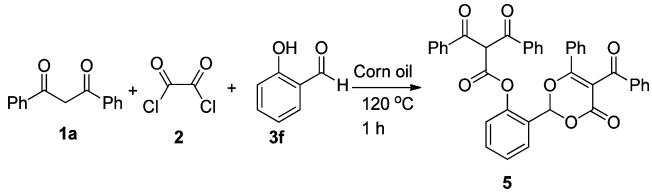
With the desired compounds in hand with good yields, we have turned our attention to new type of phenol derivative, i.e., salicyl aldehyde. The reaction between salicyl aldehyde (**3f**) and 1,3-diketo compounds in the same reaction conditions, given above, gave a dioxinone ring that has a carbonyl functional group on C_5 and aryl group on C_6 (Figure 2). In this reaction, it was found that the OH and aldehyde functionality on the benzene structure have undergone substitution and cyclization consecutively (Scheme 3).



5-acyl-6-aryl or alkyl-1,3-dioxin-4-one moiety

Figure 2. 1,3-Dioxin-4-one moiety.

Scheme 3. Synthesis of 1,3-Dioxin-4-One Bearing 1,3,3′-Tricarbonyl Moiety



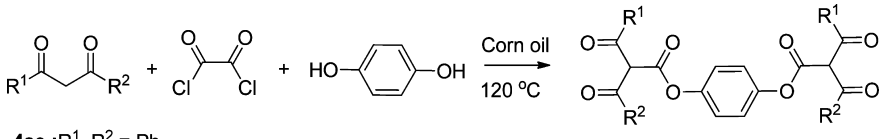
1,3-Dioxin-4-one derivatives are potential precursors for important heterocyclic compounds and phenol derivatives.[18,19] Solanoeclepin A[20] is an active natural hatching agent of the potatocyst nematode and is synthesized from 1,3-dioxin-4-one derivatives. Another example is (S)-(-)-zearalenone that is potent estrogen agonist[21] and is also obtained from 1,3-dioxin-4-one derivatives. A literature survey revealed that a 5-acyl-6-aryl-1,3-dioxin-4-one scaffold has been reported only a few times.[22−24] Nevertheless, none of procedures have been a green, multicomponent, efficient process. Moreover, we have not seen any example of the 1,3-dioxin-4-one skeleton that has the 1,3,3′-tricarbonyl moiety in the literature.

Structure **5** has been proved not only by 2D-NMR but also by single crystal X-ray (Figure 3).[25]

To the best of our knowledge, this is the first report for producing a dioxinone ring that has a 1,3,3′-tricarbonyl moiety on the same skeleton through a one-pot strategy in a green medium. The possible reaction mechanism is depicted in Scheme 4.

In our proposed reaction mechanism (Scheme 4), furandione as a reactive intermediate takes place as a result of a reaction between diketone (**1**) and oxalyl chloride (**2**). After the decomposition of furandione, 1 molecule of CO is released, and an oxoketene scaffold comes out.[26] After that, the OH group on phenol reacts with oxoketene to give compound **4**. To obtain compound **5**, the aryl group on structure **4** is salicyl aldehyde that has an aldehyde functionality that reacts with another oxoketene through the [4 + 2] Diels−Alder cycloaddition reaction. Moreover, phenol can react with oxalyl chloride to form diphenyl oxalate (**6**).[27] This reaction is reversible.

Scheme 2. C-Acylation of Diketones with Hydroquinone



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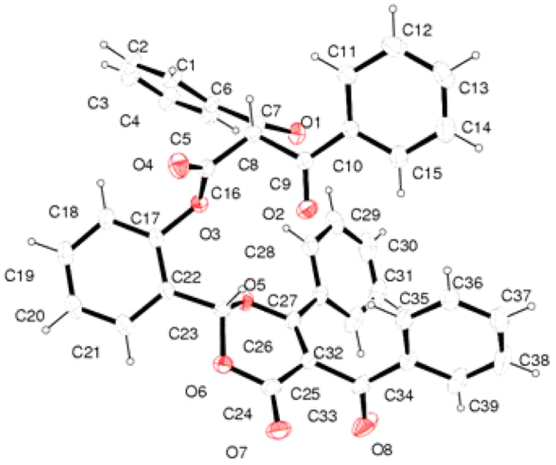
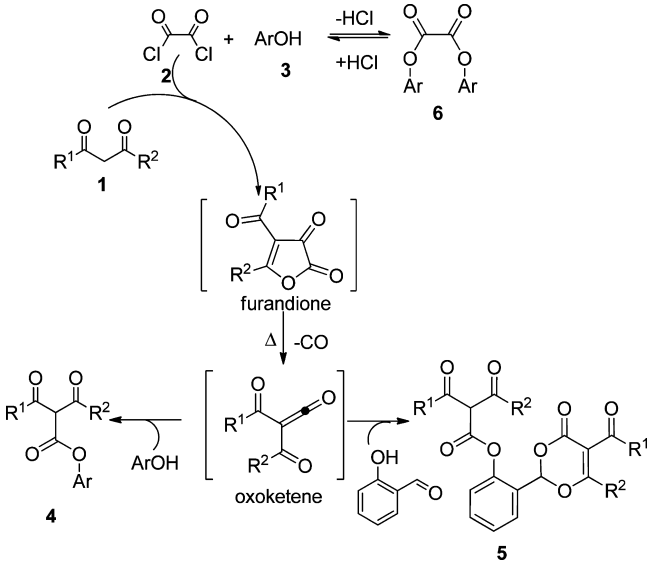


Figure 3. ORTEP drawing of molecule **5**. Thermal ellipsoids are shown at 40% probability level.

Scheme 4. Possible Reaction Mechanism for 1,3,3′-Tricarbonyl and 1,3-Dioxin-4-one



CONCLUSION

In summary, we developed a new green procedure for C-acylation of 1,3-diketones and synthesized a new type of 1,3-dioxine-4-one derivatives. This study might induce researchers performig new organic reactions to employ corn oil as the solvent. Furthermore, we believe that the type of dioxinones now accessible through the methodology presented here will prove to be valuable synthetic intermediates. Yields of the reactions are almost quantitative. For that reason, there is no need for any kind of further purification process. We are actively investigating the chemistry of these compounds and vegetable oil and will report our findings in due course.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic and analytical data of compounds, their ^{1}H NMR, ^{13}C NMR, and HRMS spectra, details of X-ray experiments, and content of vegetable oil. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

Writing of the manuscript and running of all the experiments were done by Nurettin Menges. Running of X-ray analyze was done by Ertan Şahin.

Notes

The authors declare no competing financial interest.

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DEDICATION

This article is dedicated to Prof. Dr. Metin Balci on the occasion of his 65th birthday.

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