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Highly Chemoselective Solvent-Free Synthesis of 1,3,5-Triaryl-1,5diketones: Crystallographic Investigation and Intramolecular Weak Bifurcated H Bonds Involving Aliphatic C–H Group

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^b College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, P. R. of China $\begin{array}{c} O \\ Ph \end{array} + R-CHO & \begin{array}{c} grinding \\ \hline NaOH/K_2CO_3 (1:1) \end{array} \\ Ph \end{array} \\ Ph \end{array} \\ Ph \end{array} \\ \begin{array}{c} O \\ Ph \end{array} \\ Ph \end{array} \\ \begin{array}{c} O \\ Ph \end{array} \\ Ph \end{array} \\ \begin{array}{c} O \\ Ph \end{array} \\ Ph \end{array} \\ \begin{array}{c} Ph \\ Ph \end{array} \\ \begin{array}{c} 12 \text{ examples, 75-86\% yield} \\ 12 \text{ examples, 75-86\% yield} \\ R = 2,6-Cl_2C_6H_3, 2,4-Cl_2C_6H_3, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, \\ 2-MeOC_6H_4, 4-MeOC_6H_4, 2-MeC_6H_4, 2-F_3CC_6H_4, 4-F_3CC_6H_4, \end{array}$



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Abstract Several 1,3,5-triaryl-1,5-diketones have been chemoselectively synthesized under solvent-free conditions. It was found that intramolecular weak bifurcated H-bonds interaction of aliphatic C–H group plays a decisive role in the structural arrangement of 3-(2,6-dichlorophenyl)-1,5-diphenylpentane-1,5-dione in a solid state resulting in significant impact on the corresponding bond lengths and dihedral angles.

Key words solvent-free reaction, intramolecular bifurcated weak bonds, X-ray crystallographic analysis, highly chemoselective synthesis, 1,5-diketones

From the second half of the last century, an increasing number of studies has demonstrated that various types of weak hydrogen bonds (other than conventional hydrogen bonding) are ubiquitous.¹ Particularly, weak H bonds are of great importance due to their influence on the conformation of organic compounds and 3D structure of biomacromolecules.² In 1962, the C-H-O interaction was firstly established as a hydrogen bond by Sutor based on the obtained crystallographic data.³ In 1982, Taylor and Kennard proposed two basic crystallographic characteristics of weak C-H...X (X = O, N, Cl, S) hydrogen bonds upon their systematic investigation of neutron diffraction crystal structures.⁴ These two crystallographic characteristics are as follows: 1) the distance between the proton and acceptor atoms should be shorter than the sum of their corresponding van der Waals radii,⁵ and 2) the donor-proton-acceptor angle in the H bond must be at least 90°. Since their seminal work. various compounds possessing C-H-··X (X = O, N, F, Cl, Br, etc.) weak hydrogen bonds have been discovered, and it has

been demonstrated that these weak interactions play a significant role in crystal packing,⁶ host–guest chemistry,⁷ supramolecular chirality,⁸ asymmetric organocatalysis,⁹ and biochemical phenomena.¹⁰

Also, bifurcated hydrogen bonds were found to be a key driving force to form the secondary structure of proteins.¹¹ This was firstly proposed by Albrecht and Corey upon revealing the structural disposition of NH and C=O groups in the crystal structure of α-glycine.¹² Conventional H bonds normally comprise a single donor-acceptor pair, while bifurcated H bonds include more than one donor or acceptor.¹³ Though various compounds with the bifurcated H bonds have been studied so far, most of them possessed a strong hydrogen bonding.¹⁴ However, in the case of aliphatic C-H groups, their weak acidity results in almost negligible interaction with two H-bonding acceptors simultaneously. Therefore, there are only few reports on this phenomenon to date. For example, the aromatic C-H···(F-C)₂ weak bifurcated hydrogen bonding has been described.¹⁵ Also, our group successively discovered the intramolecular weak bifurcated H bonds between aliphatic Cl and aromatic C-H as well as aliphatic C-H and aromatic Cl atoms.¹⁶

Herein we report two types of intramolecular weak bifurcated H bonds, including C=O···H–C···Cl and C–H···(Cl–C)₂, and their significant impact on changing the corresponding bond lengths and dihedral angles to fix the molecular conformation. In order to investigate this phenomenon in detail, a series of 1,3,5-triaryl-1,5-diketones have been synthesized via highly chemoselective synthesis under the solvent-free conditions. It is important to note that these compounds owing to their specific structure are often used as versatile synthetic intermediates for many heterocyclic and polyfunctional compounds.¹⁷

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In general, solvent-free reactions can not only significantly reduce the chemical waste to make synthetic transformations more environmentally benign, but also can improve the rate and selectivity of reactions.¹⁸ Our previous work demonstrated that the reaction medium had a crucial role in determining chemoselectivity of the reaction between 2,6-dichlorobenzaldehyde and acetophenone. For example, an aldol addition product **1** was obtained if this reaction was catalyzed by a 10% NaOH–EtOH solution (Scheme 1).¹⁷ However, a double-component solid-based system of K₂CO₃ and NaOH (3:1 molar ratio) under the solvent-free conditions yielded the corresponding chalcone **2a** and *syn*-head-to-head dimer of chalcone **3** (Scheme 1).¹⁵



Scheme 1 Chemoselective transformation of 2,6-dichlorobenzaldhyde with acetophenone under different conditions

Surprisingly, changing the molar ratio of K_2CO_3 and NaOH resulted in the different reaction pathway to give 3-(2,6-dichlorophenyl)-1,5-diphenylpentane-1,5-dione (**4a**) in a high yield. To continue our research, we targeted to firstly prepare chalcones via the reaction of aromatic aldehydes and acetophenone under catalysis of this double-component solid-base system. Unexpectedly, upon changing the molar ratio of the solid-base system, the reaction of 2,6-dichlorobenzaldehyde with acetophenone gave 3-(2,6-dichlorophenyl)-1,5-diphenylpentane-1,5-dione (**4a**) in a high yield.

The ¹H NMR spectrum of the product exhibited eight types of proton resonances, of which six types correspond to the aromatic protons and two sets correspond to one methine proton and four methylene protons (Figure 1, top). This spectral pattern clearly corroborates the structure of **4a**. To further confirm its structure, the crystallographic analysis of the product was carried out (Figure 1, bottom). It shows that there are two molecules of **4a** crystallizing in a typical triclinic system with *P*-1 space group.

Further insight into the crystallographic data indicated that **4a** possesses two types of the intramolecular weak bifurcated H-bonding networks. Figure 2 (top) depicts the intramolecular weak H bonds of O···C-H···Cl in **4a** with the in-



Figure 1 A fragment of the ¹H NMR (chloroform-*d*, 400 MHz) spectrum at 298 K and crystal structure of **4a**

teratomic distances between the methine proton H9 and Cl2 and O1 being 2.453 Å and 2.382 Å, correspondingly, and the bond angles for O1–H9–C9 and Cl2–H9–C9 being 120.72° and 100.07°, correspondingly. Figure 2 (bottom) represents another type of the intramolecular weak H bonds of H8B…Cl1…H10B in **4a**. In this case, the distances



Figure 2 Two types of intramolecular weak bifurcated H bonds in 4a

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from Cl1 to the methylene protons H8B and H10B are 2.597 Å and 2.836 Å, respectively, with the bond angles being 112.96° for C8–H8B–Cl1 and 129.09° for C10–H10B–Cl1. It is of note that the corresponding van der Waals radii for H,⁵ O,¹⁹ and Cl⁵ are 1.20 Å, 1.40 Å, and 1.75 Å. This clearly demonstrated the existence of intramolecular weak H bonding as O···C–H···Cl and C–H···Cl-··C–H in **4a** according to the two basic crystallographic characteristics of the weak C–H···E (E = O, N, Cl, S) H bond stated above.⁴

Further examination of the crystallographic data indicated that these bifurcated H-bonding interactions dramatically affect the C-Cl and C-O bond lengths (H-bonding acceptors) in **4a**. Hence, as shown in Figure 3, the C23-Cl1 distance is noticeably longer than that of C19-Cl2. This is because the fact that Cl1 takes part in two bifurcated weak H bonds with H8B and H10B, whilst Cl2 participates in only one weak H bond with H9 involving in weak C9-H9-Cl2 H bond.



Figure 3 Comparison of the bond length of C–O and C–Cl groups participating (blue-colored bonds) and nonparticipating (red-colored bonds) in the intramolecular weak bifurcated H bonds of **4a**

Furthermore, the bond length of C11–O2, which does not involve in the intramolecular weak H bonding, is considerable shorter than that of C7–O1, as O1 participates in formation of the H bond. These results are reasonable, since H bonding decreases the electron density of Cl and O atoms, thus inducing the elongation of the corresponding bond lengths.

Our previous work demonstrated the product diversity in the reaction between aromatic aldehyde and acetophenone catalyzed by the double-component solid-base system consisted of K₂CO₃ and NaOH.²⁰ As shown in Table 1, this reaction can yield α , β -unsaturated ketone **2a**, 1, 5-diketone 4a, and cyclohexane derivative 5a²¹ catalyzed by different composition of the double-component base. The alkali strength of the mixture plays a decisive role in the reaction pathway and the corresponding product distribution. Thus, both the >2:1 molar ratio of NaOH and K₂CO₃ and pure NaOH gave the same main product 5a (Table 1, entries 1-3). However, it is of note that using just NaOH results in formation of syrupy dope and consequent difficulty in handling the reaction. Further, upon reducing the concentration of NaOH, a mixture of 2a, 4a, and 5a was obtained (Table 1, entries 4-7). It was found that the 1:1:1 molar ratio of NaOH, K_2CO_3 , and 2,6-dichlorobenzaldehyde showed the best chemoselectivity to give **4a** as the main product in 83% yield (Table 1, entry 5). When the NaOH loading was decreased to 0.2 equiv in the solid-base mixture, only α , β -unsaturated ketone **2a** was obtained (Table 1, entry 8), as in the case of pure K_2CO_3 .





Entry	NaOH/K2CO3/ aldehyde	Product	Yield of main product (%) ^b
1	2:0:1	5a ²²	88 (84)
2	3:1:2	5a	90 (87)
3	2:1:2	5a	92 (90)
4	1:1:2	2a + 4a (main) + 5a	54 (51)
5	1:1:1	2a + 4a (main) + 5a	86 (83)
6	1:2:1	2a + 4a (main) + 5a	78 (76)
7	1:3:1	2a (main) + 4a	61 (62)
8	1:5:2	2a	(89)
9	0:2:1	2a ²⁰	(52)

^a For all the reactions, 5 mmol of 2,6-dichlorobenzenealdehyde were used at room temperature.

^b Isolated yields after recrystallization based on 2,6-dichlorobenzaldehyde at the 1:2 and 1:1.1 (in the brackets) molar ratio of 2,6-dichlorobenzaldehyde and acetophenone.

The above results clearly indicated that α , β -unsaturated ketone **2a** and 1,5-diketone **4a** are the key intermediates for the formation of cyclohexane derivative **5a**, and the reaction pathway is governed by the alkali strength of the base used. As an additional evidence of this suggestion, the corresponding control reactions of **2a** and **4a** ground in a 1:1 mixture of NaOH and K₂CO₃ condensation of 2,6-dichlorobenzenealdehyde with acetophenone provides **2a**, which in turn undergoes Michael addition reaction that yielded the single product **5a** as expected. Based on these results, a plausible mechanism was proposed (Scheme 2).

Aldol condensation of 2,6-dichlorobenzenealdehyde with acetophenone to give **4a** was performed. The second Michael addition reaction of **4a** with **2a** furnishes a linear triketone intermediate, which was not isolated. Finally, **5a** is formed via the intramolecular aldol reaction of the triketone intermediate, which occurred readily and fleetly. For-

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mation of **5a** involves multiple steps of the nucleophilic attack of a carbonyl by carbanions, while the generation of carbanions in turn is closely related to the corresponding alkali strength of the solid-base mixture. If the concentration of NaOH is decreased, the basicity is not enough to produce the corresponding carbanion, and the reaction cannot proceed further, and hence is terminated at the stage of **2a** or **4a**. This reaction mechanism is in good agreement with the experimental results obtained. With the optimized condi-

Table 2Reaction of Acetophenone with Aromatic Aldehydes underSolvent-Free Conditions a

Entry	R	Main product 4	Yield (%) ^b
1	2,6-Cl ₂ C ₆ H ₃	4a	86
2	2,4-Cl ₂ C ₆ H ₃	4b	84
3	$2-CIC_6H_4$	4c	81
4	3-CIC ₆ H ₄	4d	79
5	$4-CIC_6H_4$	4e	83
6	$2-BrC_6H_4$	4f	80
7	$2-FC_6H_4$	4g	76
8	2-MeOC ₆ H ₄	4h	75
9	4-MeOC ₆ H ₄	4i	77
10	2-MeC ₆ H ₄	4j	79
11	2-F ₃ CC ₆ H ₄	4k	83
12	$4-F_3CC_6H_4$	41	85

 a All the reactions were carried out at 5 mmol scale by using a 1:1 solid mixture of NaOH and K_2CO_3 at room temperature.

^b Yields were obtained after recrystallization for the reactions in a 1:2 molar ratio of aromatic aldehydes and acetophenone.

tions in hand and to expand the reaction scope, a series of aromatic aldehydes were allowed to react with acetophenone, as shown in Table 2. One can see that all selected aromatic aldehydes at the optimized reaction conditions resulted in the corresponding 1,5-diketone products to confirm the chemoselective efficiency of this solid-state synthetic methodology.

Further studies related to the conformational structure and weak intramolecular H-bonding interactions of this type of organic compounds are in progress and will be reported elsewhere in due course.

In summary, two types of intramolecular bifurcated weak bonds of aliphatic C–H (Cl···C···H···O and C–H···Cl···H–C) were observed in a crystal of 3-(2,6-dichlorophenyl)-1,5-diphenylpentane-1,5-dione.²³ X-ray crystallographic analysis demonstrated that the bifurcated H bonds dramatically affected the length of C–Cl and C–O bonds in the crystalline form. Furthermore, a highly chemoselective synthesis of 1,5-diketones under the solvent-free conditions was developed. This observation revealed an important role of the weak bifurcated H bonds in conformation stability and spatial structure of organic molecules.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690224.

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- (23) General Procedure

To a mixture of aromatic aldehydes (5 mmol) and acetophenone (11 mmol) a fine powder of NaOH (5 mmol) and K_2CO_3 (5 mmol) was added. The reaction mixture was ground at room temperature until it became incompact solid (generally 20–30 min). After the solid was treated with water, the water-insoluble solid was recrystallized in ethanol.

3-(2,6-Dichlorophenyl)-1,5-diphenylpentane-1,5-dione (4a) Mp 125–128 °C, 86% yield, white solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.03–7.93 (m, 4 H), 7.54 (d, *J* = 7.4 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 4 H), 7.33 (d, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.9 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 5.07 (p, *J* = 7.1 Hz, 1 H), 3.84–3.65 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ = 198.3, 138.3, 136.9, 136.7, 134.5, 133.2, 129.9, 128.9, 128.6, 128.3, 128.2, 41.1, 33.3.

Crystal Structure of Compound 4a

 $\begin{array}{l} C_{23}H_{18}Cl_{2}O_{2},\ MW=397.27,\ D_{calc}=1.342\ g/cm^{3};\ V=983.0(2)\ Å^{3}, \\ triclinic;\ Z=2;\ space\ group\ P-1,\ a=9.4157(12),\ b=10.3008(14), \\ c=10.9517(15),\ \mu\ (Mo\ K\alpha)=0.345\ mm^{-1},\ -11\le h\le 12,\ -13\le k\le 13,\ -14\le l\le 14,\ F(000)=412,\ GOF=1.059,\ T=296\ (2)\ K;\ CCDC\\ 1904249. \end{array}$