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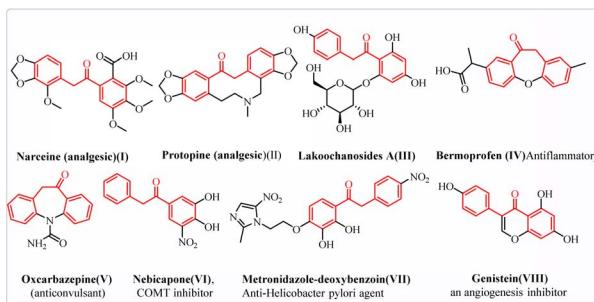
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## Introduction

Deoxybenzoins are widely recognized moieties in organic synthesis for their remarkable utility in the development of natural products and pharmaceutically active molecules (Fig. 1).<sup>1</sup> Deoxybenzoin (DOB) derivatives have demonstrated diverse biological activities, including  $\beta$ -estrogenic agonism, antiallergic, anti-inflammatory, antimicrobial, and anticancer effects.<sup>2</sup>

Additionally, deoxybenzoin serves as a key precursor for synthesizing various industrially and biologically significant compounds such as isoflavones, agrochemicals, dyes, herbicides, and fire-resistant polymers.<sup>3</sup> It is also a versatile structural moiety for the construction of heterocyclic compounds like pyrimidinones, quinoxalines, and indoles.<sup>4</sup> However, their synthetic flexibility and capability to undergo facile trans-



**Fig. 1** Biologically active moieties containing deoxybenzoin building block

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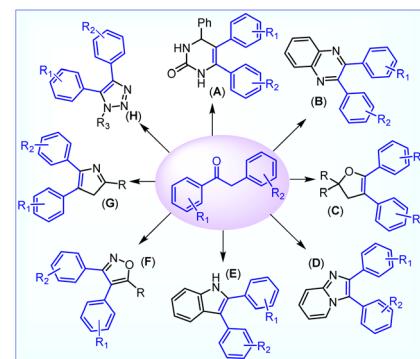
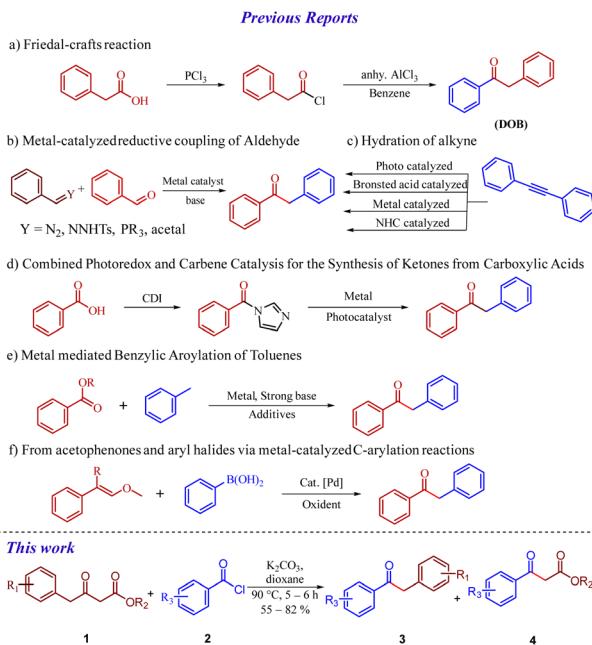


Fig. 2 Synthetic utility of deoxybenzoins.



Scheme 1 Previous reports and present work.

molecular oxygen as an oxidant,<sup>13</sup> have further enhanced the synthetic utility of deoxybenzoins.

Recent investigations have introduced several innovative methodologies for deoxybenzoin synthesis. These include alkyne hydration catalyzed by *N*-heterocyclic carbene-based gold complexes,<sup>14</sup> the reaction of non-stabilized diazoalkanes with aldehydes in the presence of  $\text{Sc}(\text{OTf})_3$ ,<sup>15</sup> and the integration of photoredox catalysis with carbene chemistry to achieve reductive single-electron alkylation of acyl azoliums, enabling ketone synthesis from carboxylic acids (Scheme 1d).<sup>16</sup> Additional strategies have involved the benzylic arylation of toluene mediated by  $\text{LiN}(\text{SiMe}_3)_2$  with  $\text{CsF}$  as an additive, as well as transformations involving *N*-methoxy-*N*-methylbenzamide and methyl benzoate derivatives (Scheme 1e).<sup>17</sup> Furthermore, metal-catalyzed Heck coupling reactions have also been reported for deoxybenzoin synthesis (Scheme 1f).<sup>18</sup> Despite these advancements, challenges such as high reaction temperatures, reliance on metal catalysts, functional group incompatibility, and the need for supplementary acid catalysts still persist. Direct, simple, and cost-effective synthetic methods for deoxybenzoin remain scarce in the literature.

To address this gap, we report a new synthesis method for deoxybenzoin derivatives through a base-mediated dual acylation reaction of  $\gamma$ -aryl  $\beta$ -keto ester. This methodology involves the addition under mild conditions, simplifying the synthetic pathway and avoiding the need for metals, additives, and ligands. The reaction proceeds *via* the nucleophilic addition-elimination mechanism, where the base effectively facilitates the concerted reaction, resulting in the formation of the desired deoxybenzoin derivatives. The mild reaction conditions minimize side reactions and ensure compatibility with a wide range of functional groups, making the process versatile and scalable. Additionally, the cost-effectiveness of this approach stems from

its reliance on readily available starting materials and the elimination of expensive catalysts or reagents. This innovative strategy provides a significant advancement in the field by addressing the limitations of existing methods and offering an environment-friendly alternative for the efficient synthesis of deoxybenzoin.

## Result and discussion

The investigation and optimization of products **3a** and **4a** were carried out using methyl 3-oxo-4-(2,4,5-trifluorophenyl) butanoate **1a** as the model substrate and benzoyl chloride (**2a**) as the model reactive partner. The screening of organic and inorganic bases was carried out in dioxane solvent at room temperature. After some initial trials, the reaction time was set for 12 h. Various organic bases such as 8-Diazabicyclo[5.4.0]undec-7-ene

Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Base	Solvent	$T$ (°C)	Time (h)	Yield <sup>b</sup> %	
					(3a)	(4a)
1	DABCO <sup>c</sup>	Dioxane <sup>d</sup>	Rt <sup>e</sup>	12	NR	NR
2	DBU <sup>f</sup>	Dioxane	Rt	12	NR	NR
3	NET <sub>3</sub>	Dioxane	Rt	12	24	18
4	K <sub>3</sub> PO <sub>4</sub>	Dioxane	Rt	12	25	22
5	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	Rt	12	20	15
6	NaOH	Dioxane	Rt	12	0	0
7	NaOMe	Dioxane	Rt	12	0	0
8	K <sub>2</sub> CO <sub>3</sub>	Dioxane	Rt	12	30	25
9	K <sub>2</sub> CO <sub>3</sub>	Dioxane	55	12	35	30
10	K <sub>2</sub> CO <sub>3</sub>	Dioxane	75	12	44	40
11	K <sub>2</sub> CO <sub>3</sub>	Dioxane	90	6	82	15
12	K <sub>2</sub> CO <sub>3</sub>	Dioxane	90	3	50	20
13	K <sub>2</sub> CO <sub>3</sub>	Xylene	90	6	50	35
14	K <sub>2</sub> CO <sub>3</sub>	Toluene	90	6	40	50
15	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	90	6	26	28
16	K <sub>2</sub> CO <sub>3</sub>	Acetone	90	6	32	18
17	K <sub>2</sub> CO <sub>3</sub>	Dioxane	90	24	82	15
18	NET <sub>3</sub>	Dioxane	60	12	28	14
19	NET <sub>3</sub>	Dioxane	80	12	30	15
20	NET <sub>3</sub>	Dioxane	90	12	30	15
21	NET <sub>3</sub>	Dioxane	100	12	31	15
22	K <sub>3</sub> PO <sub>4</sub>	Dioxane	60	12	34	16
23	K <sub>3</sub> PO <sub>4</sub>	Dioxane	80	12	55	20
24	K <sub>3</sub> PO <sub>4</sub>	Dioxane	90	12	60	18
25	K <sub>3</sub> PO <sub>4</sub>	Dioxane	100	12	65	15
26	K <sub>2</sub> CO <sub>3</sub>	Dioxane	100	12	82	15

<sup>a</sup> Reaction conditions: For (entries 1–7) **1a** (0.4062 mmol, 1 equiv.) and **2a** (0.4062 mmol, 1 equiv.),  $\text{K}_2\text{CO}_3$  (0.4062 mmol, 1 equiv.) in dioxane solvent (2 ml), for (entries 8–10) **1a** (0.4062 mmol, 1 equiv.) and **2a** (0.6093 mmol, 1.5 equiv.),  $\text{K}_2\text{CO}_3$  (0.6093 mmol, 1.5 equiv.) in dioxane solvent (2 ml), for (entries 11–17) **1a** (0.4062 mmol, 1 equiv.) and **2a** (0.8124 mmol, 2 equiv.),  $\text{K}_2\text{CO}_3$  (0.8124 mmol, 2 equiv.) in dioxane solvent (2 ml). <sup>b</sup> Isolated yield. <sup>c</sup> 1,4-diazabicyclo[2.2.2]octane. <sup>d</sup> 1,4-dioxane. <sup>e</sup> Room temperature. <sup>f</sup> 8-diazabicyclo[5.4.0]undec-7-ene.

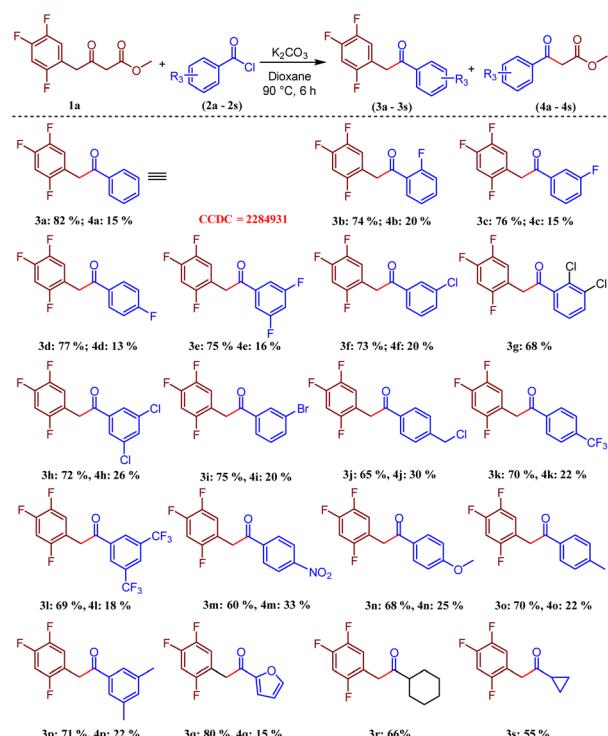
undec-7-ene (DBU), triethylamine ( $\text{Et}_3\text{N}$ ) and 1,4-diazabicyclo[2.2.2]octane (DABCO), as well as inorganic bases like  $\text{NaOH}$  and  $\text{NaOMe}$ , had been tested under standard reaction conditions in dioxane, and the results are summarized in Table 1.

No reaction was observed when 8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) had been used (Table 1, entries 1 and 2). However, in the presence of triethylamine in dioxane at room temperature for 12 h, the corresponding products **3a** and **4a** were observed to yield 24% and 18%, respectively (Table 1, entry 3).  $\text{K}_3\text{PO}_4$ ,  $\text{Cs}_2\text{CO}_3$  yielded the desired products with low to moderate yields (Table 1, entries 4 to 5). No product formation was observed using strong bases such as  $\text{NaOH}$  and  $\text{NaOMe}$  (Table 1, entries 6 to 7). Surprisingly,  $\text{K}_2\text{CO}_3$  had proved to be the most effective inorganic base in dioxane solvent compared to the other bases. Moreover, increasing the temperature, the yields of products **3a** and **4a** have increased (as shown in Table 1, entries 9 to 11). Therefore, the reaction conditions were further optimized at 90 °C. Finally, it was found that using 2 equiv. of benzoyl chloride (**2a**) and 2 equiv. of  $\text{K}_2\text{CO}_3$  is sufficient to generate the desired product **3a** in 82% and the minor product **4a** in 15% isolated yield at 90 °C for 6 h (Table 1, entry 11), representing our best result. Common organic non-polar and polar aprotic solvents such as toluene, xylene, DMF, DMSO, MeCN, and acetone resulted in lower yields (Table 1, entry 14 to 16) and dioxane was found to be the best solvent for our desired product formation. The stability of product **3a** was examined under prolonged reaction times, revealing no impact on its stability under the reaction conditions (Table 1, entry 17).

We evaluated  $\text{K}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ , and  $\text{NEt}_3$  at 60, 80, 90, and 100 °C, with reactions at 100 °C conducted in sealed vials to prevent solvent loss. The results indicate that: (i)  $\text{K}_3\text{PO}_4$  showed enhanced conversion at elevated temperatures, achieving a maximum isolated yield of 65% at 100 °C (Table 1, entry 25). (ii)  $\text{NEt}_3$  remained ineffective above room temperature, likely due to its lower basicity and limited solubility in dioxane (Table 1, entry 18 to 21) and (iii)  $\text{K}_2\text{CO}_3$  displayed performance consistent with previous observations (Table 1, entry 26) with an optimum yield obtained at 90 °C. Overall, these results reveal a modest temperature-dependent base effect and support  $\text{K}_2\text{CO}_3$  at 90 °C as the optimal reaction condition.

With the optimized reaction conditions established, we investigated the substrate scope, focusing on methyl 3-oxo-4-(2,4,5-trifluorophenyl)butanoate (Table 2).  $\gamma$ -aryl- $\beta$ -ketoesters reacted with ortho-, meta-, and *para*-fluoro-substituted benzoyl chlorides (**2b**–**2d**), yielded the corresponding products **3b**–**3d** in 74–77% yields. Similarly, 3,5-difluorobenzoyl chloride (**2e**) produced the product 1-(3,5-difluorophenyl)-2-(2,4,5-trifluorophenyl)ethan-1-one (**3e**) in 75% yield. Halosubstituted derivatives of 1-phenyl-2-(2,4,5-trifluorophenyl)ethan-1-one (**1a**), where chloro- and bromo-containing benzoyl chlorides (**2f**–**2i**) were employed and delivered the desired deoxybenzoin derivatives **3f**–**3i** in good yields. Furthermore, benzoyl chlorides bearing electron-withdrawing groups, such as 4- $\text{CH}_2\text{Cl}$ , 4- $\text{CF}_3$ , 3,5-di $\text{CF}_3$ - and 4- $\text{NO}_2$ -containing benzoyl chlorides (**2j**–**2m**) produced our desired products **3j**–**3m** with very good yields. In addition, benzoyl chlorides containing electron-donating groups, including 4- $\text{OMe}$ , 4- $\text{Me}$ , and 3,5-

Table 2 Substrate scope of methyl 3-oxo-4-(2,4,5-trifluorophenyl)butanoate with various benzoyl chlorides. Reaction conditions: **1a** (0.8124 mmol, 1 equiv.) and **2a**–**2s** (1.62 mmol, 2 equiv.),  $\text{K}_2\text{CO}_3$  (1.62 mmol, 2 equiv.) were stirred in dioxane (3 ml) under Ar at 90 °C for 6 h



DiMe (**2n**–**2p**), furnished the products **3n**–**3p** in 68–71% yields, respectively. Interestingly, the electronic effect of the substituents did not significantly impact the reaction outcomes (Table 2, entries **3b**–**3p**). Additionally, furan-2-carbonyl chloride (**2q**) provided an excellent yield of 80%, while using cyclohexanecarbonyl chloride (**2r**) and cyclopropanecarbonyl chloride (**2s**) resulted in moderate yields of 66 and 55%, respectively.

During our investigation, we observed that certain benzoyl chlorides showed no reactivity toward the formation of the desired deoxybenzoin (Fig. 3). For instance, electron-rich derivatives such as **2u** and **2v**, as well as the electron-deficient 4-cyanobenzoyl chloride (**2w**), and heteroaromatic acyl

chlorides including isonicotinoyl chloride hydrochloride (**2x**) and nicotinoyl chloride hydrochloride (**2y**), failed to yield the target products. Similarly, aryl substrates bearing electron-donating groups, such as **1j** and **1k**, were also unproductive under the optimized conditions (Fig. 3).

Further, we investigated the reaction of various  $\gamma$ -aryl- $\beta$ -ketoesters with differently substituted benzoyl chlorides under optimized conditions (Table 3). When methyl 3-oxo-4-phenylbutanoate (**1b**) was treated with various benzoyl chlorides (**2a**, **2e**, **2i**, **2p**), yielding the corresponding products **3t**–**3w** in 65 to 67%, respectively. These results demonstrated the broad compatibility of the reaction with benzoyl chlorides bearing diverse substituents. Similarly, methyl 4-(4-fluorophenyl)-3-oxo butanoate (**1c**) was reacted with 3,4-dimethoxybenzoyl chloride (**2t**), furan-2-carbonyl chloride (**2q**), and cyclohexanecarbonyl chloride (**2r**), affording products **3x**, **3y**, and **3z** in yields of 67, 73, and 55%, respectively. These results highlighted the ability of the reaction to tolerate both aromatic and aliphatic acylating agents. Additionally, methyl 4-(2-chlorophenyl)-3-oxo butanoate (**1d**) was tested with 3,5-dimethylbenzoyl chloride (**2p**), yielded the corresponding product **3aa'** in 60%, showcasing compatibility with electron-donating substituents on the benzoyl chloride (Table 3). However,

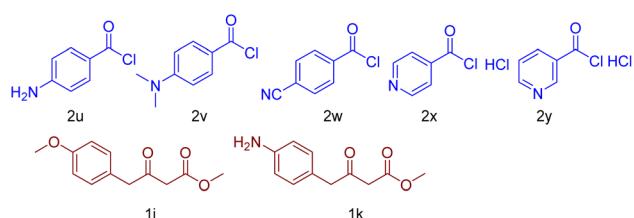
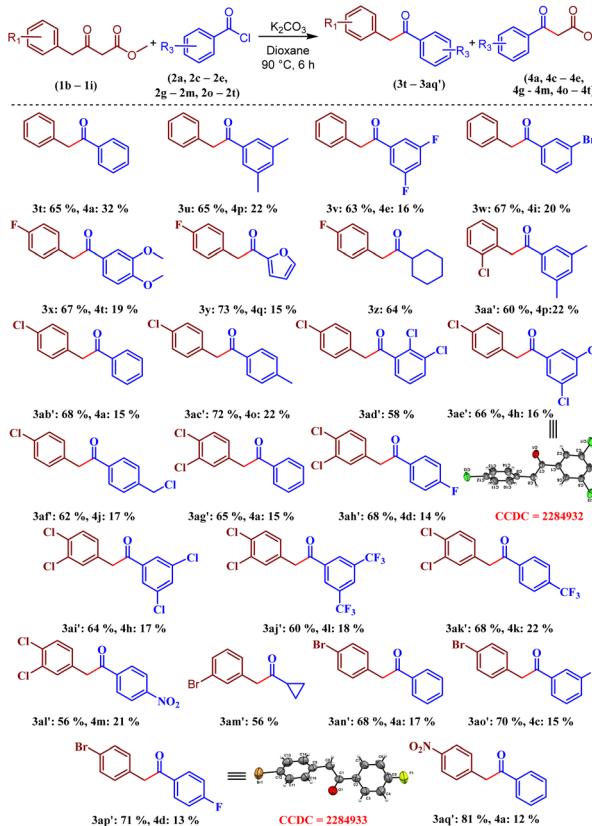


Fig. 3 2-Chloropyridines, which were unproductive under the optimized reaction conditions.

Table 3 Substrate scope for the synthesis of deoxybenzoins reaction conditions for **1b** (1.04 mmol, 1 equiv.) and **2a**, **2p**, **2e**, **2w** (2.08 mmol, 2 equiv.),  $K_2CO_3$  (1.62 mmol, 2 equiv.), for **1c** (0.9514 mmol), **2t**, **2q**, **2r** (1.9 mmol, 2 equiv.),  $K_2CO_3$  (1.9 mmol, 2 equiv.), for **1d**–**1e** (0.8824 mmol) **2a**, **2o**, **2g**, **2h**, **2j**, **2p** (1.76 mmol, 2 equiv.),  $K_2CO_3$  (1.76 mmol, 2 equiv.), **1f** (0.766 mmol), **2a**, **2d**, **4h**, **4i**, **2k**, **2l**, **2m** (1.53 mmol, 2 equiv.),  $K_2CO_3$  (1.53 mmol, 2 equiv.), **1g**–**1h** (0.7377 mmol), **2a**, **2c**, **2d** (1.48 mmol, 2 equiv.),  $K_2CO_3$  (1.48 mmol, 2 equiv.), **1i** (0.8431 mmol, 2 equiv.), **2a** (1.69 mmol, 2 equiv.)  $K_2CO_3$  (1.69 mmol, 2 equiv.) were stirred in dioxane (3 ml) under Ar at 90 °C for 6 h

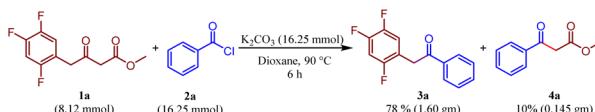


methyl 4-(4-chlorophenyl)-3-oxobutanoate (**1e**) exhibited excellent reactivity with a range of benzoyl chlorides (**2a**) including 4-Me (**2o**), 2,3-dichloro (**2g**), 3,5-dichloro (**2h**), and 4-CH<sub>2</sub>Cl (**2j**) substituents, producing the corresponding products **3ab'** to **3af'** with very good yields. This range of reactivity emphasized the adaptability of the substrate to various functional groups.

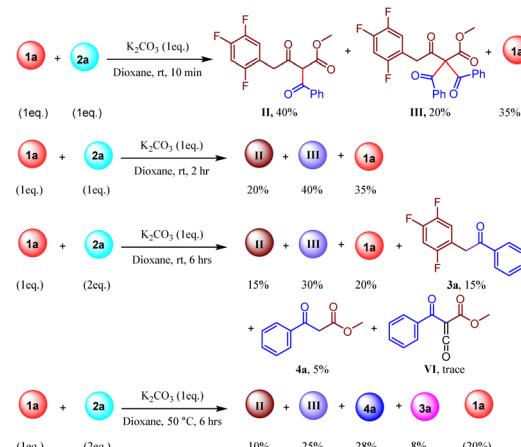
Further to our delight, various benzoyl chlorides (**2a**, **2d**, **2h**, **2k**, **2l**, **2m**) also participated with methyl 4-(3,4-dichlorophenyl)-3-oxobutanoate (**1f**) in the reactions and provided the desired deoxybenzoins **3ag'-3al'** in 59–68% yield (Table 3). These reactions demonstrated the method's efficiency in accommodating electron-withdrawing groups on the benzoyl chloride. Moreover, methyl 4-(3-bromophenyl)-3-oxo butanoate (**1g**) reacted with cyclopropanecarbonyl chloride (**2s**) to yield product **3am'** in 56%, indicating moderate compatibility with alicyclic carbonyl chloride. Similarly, Methyl 4-(4-bromophenyl)-3-oxobutanoate (**1h**) successfully reacted with **2a**, **2c**, and **2d** to afford products **3an'** to **3ap'** with moderate to good yields. Finally, methyl 4-(4-nitrophenyl)-3-oxobutanoate (**1i**) reacted with benzoyl chloride (**2a**) to produce 2-(4-nitrophenyl)-1-phenylethan-1-one (**3aq'**) with the yield of 81% (Table 3). These results further underscored the reaction's tolerance to halogen-substituted benzoyl chlorides and its potential for generating high yields with substrates bearing diverse functional groups.

To evaluate the synthetic practicality of this one-pot reaction, we performed a gram-scale reaction (Scheme 2) using **1a** and **2a** on an 8.12 mmol scale (Scheme 2). The reaction successfully yielded **3a** with an isolated yield of 78%. This result confirms the method's reproducibility on a larger scale, offering a feasible protocol for potential industrial applications.

To gain a deeper understanding of the reaction mechanism, a series of control experiments were performed using substrates **1a** and **2a** under different temperatures and reagent stoichiometries. When **1a** was treated with an equimolar amount of **2a** and K<sub>2</sub>CO<sub>3</sub> at room temperature, intermediate **II** was formed in 40% yield and intermediate **III** in 20% yield within 10 minutes, along with unreacted **1a**, as confirmed by NMR and mass spectrometry (see SI). Extending the reaction time to 2 hours under the same conditions resulted in a decrease in intermediate **II** and a corresponding increase in intermediate **III**, suggesting the transformation of **II** into **III** (Scheme 3). Further continuation of the reaction for 6 hours using 2 equivalents each of **2a** and K<sub>2</sub>CO<sub>3</sub> resulted in the formation of the desired products **3a** and **4a**, along with decreased amounts of intermediates **II** and **III**, and trace amount of the intermediate **VI**, as confirmed by HRMS. When the same reaction was carried out at 50 °C for 6 h, an increased yield of **3a** and **4a** was observed (Scheme 3).

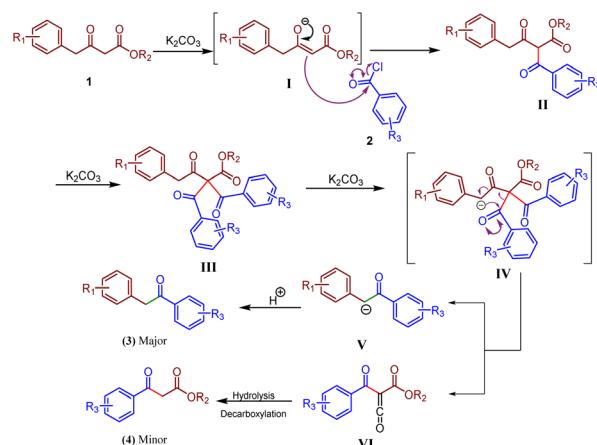


Scheme 2 Gram-scale synthesis of compound **3a**.



Scheme 3 Control experiment.

The proposed reaction mechanism as shown in Scheme 4, was supported by our control experiments and relevant literature precedents. Initially, K<sub>2</sub>CO<sub>3</sub> deprotonates the  $\alpha$ -carbon of the  $\beta$ -keto ester, generating enolate **I**. This enolate undergoes a base-promoted nucleophilic acyl substitution with the benzoyl chloride (**2a**), resulting in the formation of intermediate **II**. Intermediate **II** was successfully isolated and characterized by NMR and HRMS (see SI). In the presence of excess K<sub>2</sub>CO<sub>3</sub>, a second deprotonation at the  $\alpha$ -position occurs, enabling a subsequent nucleophilic attack on a second equivalent of benzoyl chloride to form intermediate **III**. Another deprotonation of intermediate **III** generates a carbanion, which undergoes an intramolecular nucleophilic attack on a neighbouring carbonyl group, leading to the formation of intermediate **IV**. This species then undergoes a concerted transformation to afford the thermodynamically stable compound **V**, along with a trace amount of species **VI**. Protonation of compound **V** furnishes the major product, deoxybenzoin derivative **3**. In contrast, intermediate **VI** undergoes *in situ* hydrolysis<sup>19</sup> followed by thermal decarboxylation,<sup>20</sup> giving rise to the minor  $\beta$ -ketoester product **4**.



Scheme 4 Proposed reaction mechanism.



## Conclusion

We have developed an efficient and operationally simple method for the synthesis of deoxybenzoin derivatives *via* a base-promoted fragmentation of  $\gamma$ -aryl- $\beta$ -ketoesters in the presence of benzoyl chloride *via* concerted mechanism. The protocol tolerates a broad range of functional groups and delivers the corresponding products in good to excellent yields under mild reaction conditions. The method benefits from the use of easily accessible starting materials and straightforward reaction setup, offering a valuable synthetic route to the deoxybenzoin scaffold. Given the prevalence of this motif in biologically active natural products and pharmaceuticals, the reported strategy may find broad application in synthetic and medicinal chemistry.

## Experimental procedure

### General procedure A

Methyl 3-oxo-4-(2,4,5-trifluorophenyl)butanoate (0.8124 mmol, 1 equiv.) was stirred with the potassium carbonate (1.62 mmol, 2 equiv.) in 1,4-dioxane (3 mL) at room temperature for 5 min. Benzoyl Chloride (1.6247 mmol, 2 equiv.) was added slowly drop-wise, and the reaction mixture was stirred at 90 °C until benzoyl chloride was completely consumed (monitored by TLC). Typically starting materials were fully consumed within 5 hours. After 6 hours, the reaction mixture was diluted with ethyl acetate, saturated aqueous sodium chloride solution, and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography. The resulting product was then analyzed by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, LC-MS/MS and HRMS to verify the identity and purity.  $^{19}\text{F}$  NMR was also reported in the case that compounds have fluorine atom(s).

## Author contributions

S. S. C. and B. S. designed the project. B. S. received the research funding, accommodated researchers, supervised all the work. S. S. C. performed the reaction and characterized all the products. R. S. D. and G. R. K. helped with the formal analysis of the samples. The manuscript and the ESI were prepared mutually by all authors.

## Conflicts of interest

The authors declare no competing financial interest.

## Data availability

The starting materials (**1a–1h**)<sup>21</sup> and **1i** (ref. 22) were synthesized from a known literature procedure. The starting materials **2a–2t** were commercially available.

CCDC 2284931–2284933 contain the supplementary crystallographic data for this paper.<sup>23</sup>

**Supplementary information:** Full experimental details, copies of spectral data, structures, X-ray crystal structures, and crystallographic data (CIF). See DOI: <https://doi.org/10.1039/d5ra05242d>.

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