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Base mediated approach for the synthesis of deoxybenzoins using γ -aryl- β -ketoesters and benzoyl chlorides

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This study introduces a one-pot, transition metal-free strategy for synthesizing deoxybenzoins, overcoming the challenges of conventional methods. The reaction involves dual acylation of γ -aryl β -keto esters using K₂CO₃ in dioxane at 90 °C, followed by a concerted transformation to form deoxybenzoin. The protocol operates under mild conditions, tolerates a broad range of substrates, and produces minimal byproducts, making it a practical, scalable alternative for accessing pharmaceutically relevant deoxybenzoins.

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).1 Deoxybenzoin (DOB) derivatives have demonstrated diverse biological activities, including β-estrogenic agonism, antiallergic, anti-inflammatory, antimicrobial, and anticancer effects.2

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.3 It is also a versatile structural moiety for the construction of heterocyclic compounds like pyrimidinones, quinoxalines, and indoles.4 However, their synthetic flexibility and capability to undergo facile trans-

Fig. 1 Biologically active moieties containing deoxybenzoin building block

formation to a wide range of functional groups made them valuable building blocks in organic synthesis (Fig. 2).5

The conventional method for the synthesis of deoxybenzoins involves a Friedel-Crafts reaction and requires the prefunctionalization of phenylacetic acid to phenylacetyl chloride using a harsh chlorinating agent, hence affecting process efficiency (Scheme 1a).6 To overcome these challenges, various strategies have been developed, such as employing substrates with internal multifunctional groups (e.g., diazonium, sulfonyl hydrazone, and phosphorus ylide) (Scheme 1b)⁷ or using metal reagents like RMgBr and R3Al.8 These approaches reduced the multistep operations but did not depend on the external metal catalysts, additives, and prefunctionalized substrates.

Among advanced methodologies, metal-catalyzed hydration of alkynes and Brønsted acid or photocatalyzed alkyne hydration has shown a promising approach (Scheme 1c).9 Similarly, the Wacker process has proven valuable for synthesizing ketones from terminal or 1,2-disubstituted alkenes via olefin oxidation.10 Other modifications, such as electrochemical oxidation,11 metal-catalyzed oxidation,12 and the use of

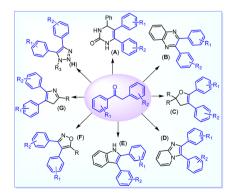
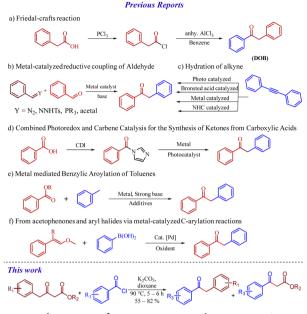


Fig. 2 Synthetic utility of deoxybenzoins.

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Paper



Scheme 1 Previous reports and present work

molecular oxygen as an oxidant,¹³ 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,14 the reaction of non-stabilized diazoalkanes with aldehydes in the presence of Sc(OTf)₃, ¹⁵ 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).16 Additional strategies have involved the benzylic arylation of toluene mediated by LiN(SiMe₃)₂ with CsF as an additive, as well as transformations involving N-methoxy-N-methylbenzamide and methyl benzoate derivatives (Scheme 1e).17 Furthermore, metalcatalyzed Heck coupling reactions have also been reported for deoxybenzoin synthesis (Scheme 1f).18 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 γ -aryl β -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 \emph{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]

Table 1 Optimization of reaction conditions

					Yield ^b %	
Entry	Base	Solvent	T (°C)	Time (h)	(3a)	(4a)
1	DABCO^{c}	Dioxane ^d	Rt^e	12	NR	NR
2	DBU^f	Dioxane	Rt	12	NR	NR
3	NEt_3	Dioxane	Rt	12	24	18
4	K_3PO_4	Dioxane	Rt	12	25	22
5	Cs_2CO_3	Dioxane	Rt	12	20	15
6	NaOH	Dioxane	Rt	12	0	0
7	NaOMe	Dioxane	Rt	12	0	0
8	K_2CO_3	Dioxane	Rt	12	30	25
9	K_2CO_3	Dioxane	55	12	35	30
10	K_2CO_3	Dioxane	75	12	44	40
11	K_2CO_3	Dioxane	90	6	82	15
12	K_2CO_3	Dioxane	90	3	50	20
13	K_2CO_3	Xylene	90	6	50	35
14	K_2CO_3	Toluene	90	6	40	50
15	K_2CO_3	CH_3CN	90	6	26	28
16	K_2CO_3	Acetone	90	6	32	18
17	K_2CO_3	Dioxane	90	24	82	15
18	NEt_3	Dioxane	60	12	28	14
19	NEt_3	Dioxane	80	12	30	15
20	NEt_3	Dioxane	90	12	30	15
21	NEt_3	Dioxane	100	12	31	15
22	K_3PO_4	Dioxane	60	12	34	16
23	K_3PO_4	Dioxane	80	12	55	20
24	K_3PO_4	Dioxane	90	12	60	18
25	K_3PO_4	Dioxane	100	12	65	15
26	K_2CO_3	Dioxane	100	12	82	15

^a Reaction conditions: For (entries 1–7) **1a** (0.4062 mmol, 1 equiv.) and **2a** (0.4062 mmol, 1 equiv.), K_2CO_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.), K_2CO_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.), K_2CO_3 (0.8124 mmol, 2 equiv.) in dioxane solvent (2 ml). ^b Isolated yield. ^c 1,4-diazabicyclo[2.2.2]octane. ^d 1,4 – dioxane. ^e Room temperature. ^f 8-diazabicyclo[5.4.0]undec-7-ene.

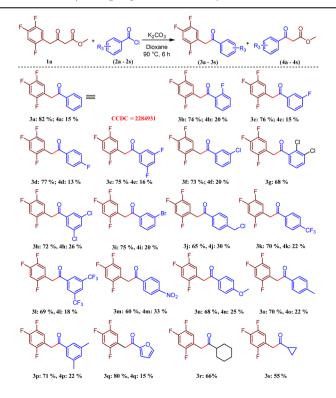
undec-7-ene (DBU), triethylamine (Et_3N) and 1,4-diazabicyclo [2.2.2]octane (DABCO), as well as inorganic bases like NaOH and NaOMe, had been tested under standard reaction conditions in dioxane, and the results are summarized in Table 1.

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). K₃PO₄, Cs₂CO₃ 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 NaOH and NaOMe (Table 1, entries 6 to 7). Surprisingly, K₂CO₃ 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 K₂CO₃ 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 K_2CO_3 , K_3PO_4 , and 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) K_3PO_4 showed enhanced conversion at elevated temperatures, achieving a maximum isolated yield of 65% at 100 °C (Table 1, entry 25). (ii) 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) K_2CO_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 K_2CO_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). γ-aryl-β-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-(2,4,5trifluorophenyl)ethan-1-one in 75% vield. Halo-(3e) substituted 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-CH₂Cl-, 4-CF₃-, 3,5-diCF₃- and 4-NO₂- 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-OMe, 4-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.), K₂CO₃ (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.

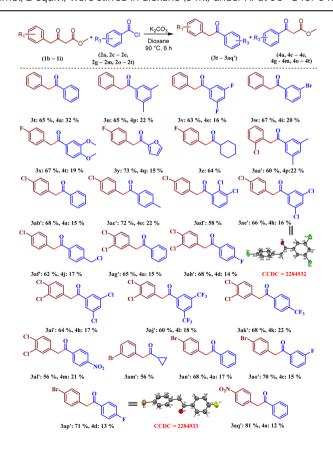
During our investigation, we observed that certain benzoyl chlorides showed no reactivity toward the formation of the desired deoxybenzoin (Fig. 3). For instance, electron-rich derivatives such as **2u** and **2v**, as well as the electron-deficient 4-cyanobenzoyl chloride (**2w**), and heteroaromatic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

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

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

Further, we investigated the reaction of various γ-aryl-βketoesters with differently substituted benzoyl chlorides under optimized conditions (Table 3). When methyl 3-oxo-4phenylbutanoate (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 diverse substituents. Similarly, methyl bearing fluorophenyl)-3-oxo butanoate (1c) was reacted with 3,4-dimethoxybenzovl 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,

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 (1.77 mmol), 2a, 2c, 2d (1.48 mmol, 2 equiv.), K_2CO_3 (1.48 mmol, 2 equiv.), K_2CO_3 (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



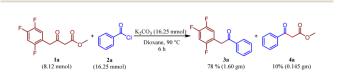
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methyl 4-(4-chlorophenyl)-3-oxobutanoate (1e) exhibited excellent reactivity with a range of benzovl chlorides (2a) including 4-Me (20), 2,3-dichloro (2g), 3,5-dichloro (2h), and 4-CH₂Cl (2j) substituents, producing the corresponding products 3ab' 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)-3oxobutanoate (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 benzovl chloride (2a) to produce 2-(4-nitrophenyl)-1phenylethan-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 K₂CO₃ 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 K2CO3 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, K₂CO₃ deprotonates the α-carbon of the β-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 K₂CO₃, a second deprotonation at the α-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 hydrolysis19 followed by thermal decarboxylation,20 giving rise to the minor βketoester product 4.

Proposed reaction mechanism. Scheme 4

Paper

Conclusion

We have developed an efficient and operationally simple method for the synthesis of deoxybenzoin derivatives via a basepromoted fragmentation of γ -aryl- β -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 Na₂SO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography. The resulting product was then analyzed by ¹H NMR, ¹³C NMR, LC-MS\MS and HRMS to verify the identity and purity. 19F 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)21 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.23

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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