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A catalyst-free, facile and efficient approach to cyclic esters: synthesis of 4*H*-benzo[*d*][1,3]dioxin-4-ones†

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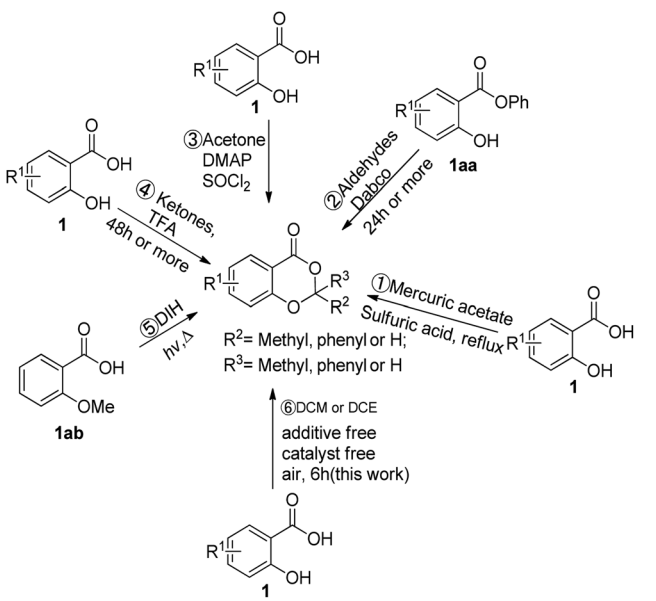
We have developed a green and practical method to construct 4*H*-benzo[*d*][1,3]dioxin-4-one and its derivatives, which are important structural units in insecticides, and intermediates to synthesize multiple-substituted benzene derivatives of great value. The catalyst- and additive-free conditions, commercial and cheap starting materials and short reaction time, make this transformation practical and attractive.

Introduction

4*H*-Benzo[*d*][1,3]dioxin-4-one and its derivatives show great promise for many applications in organic and pharmaceutical synthesis[1–23] as well as agriculture.[24] However, few methodologies exist for building these structures so far. In a pioneering work, Mowry and co-workers obtained 4*H*-benzo[*d*][1,3]dioxin-4-ones from the condensation of salicylic acids with vinyl acetate, catalyzed by mercuric acetate in the presence of sulfuric acid (①, Scheme 1).[25,26] To avoid using sulfuric acid or metal magma, more convenient methodologies have been developed. For instance, Perlmutter and co-workers discovered that the reaction of phenyl salicylate with aldehydes could afford the corresponding cyclic products using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in 1996 (②, Scheme 1).[27] Salicylic acids can be converted into 4*H*-benzo[*d*][1,3]-dioxin-4-ones by reacting with a ketone, catalyzed by *N*,*N*-4-dimethylamino-pyridine (DMAP) in the presence of stoichiometric $SOCl_2$ (③, Scheme 1)[8–19,28,29] and in a solution of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (④, Scheme 1).[5,20–22] Instead of TFA and trifluoroacetic anhydride, catalytic amounts of sulfuric acid (H_2SO_4) and stoichiometric acetic anhydride can be used to prompt this transformation.[23] Gandelman and co-workers accidentally produced 4*H*-benzo[*d*][1,3]dioxin-4-one *via* irradiation of a mixture containing *o*-methylsalicylic acid, 1,3-diiodo-5,5-dimethylhydantoin (DIH) and dichloroethane for 20 h under reflux (⑤, Scheme 1).[30]

However, some challenges still exist in these procedures, such as unavailable starting materials, limitations of substrate scope, unavoidable side reactions and the requirement for strong acids. Therefore, a green, practical and efficient approach for the formation of 4*H*-benzo[*d*][1,3]dioxin-4-one and its derivatives from readily available starting materials is extremely desirable. Herein, we present an unprecedented protocol to construct such a structure (⑥, Scheme 1). The significance of this methodology is that: (1) CH_2Cl_2, a common and cheap reagent in laboratories, has seldom been used as a reagent and C1 source at the same time;[31,32] (2) additive and



Scheme 1 Strategies for the synthesis of 4*H*-benzo[*d*][1,3]dioxin-4-ones.

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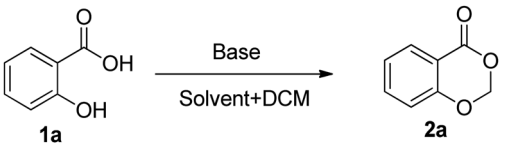
metal free reaction conditions were used; (3) moisture insensitivity and high efficiency were achieved.

Results and discussion

Initially, the reaction of salicylic acid (**1a**) with CH_2Cl_2 was chosen as a model reaction to screen the reaction parameters. $K_3PO_4 \cdot 3H_2O$ was investigated first to screen the reaction temperature and solvent. Only a trace amount of the desired product was observed at 60 °C (Table 1, entry 1). When the temperature was raised to 80 °C, the desired product **2a** was achieved in 10% yield (Table 1, entry 2). The yield increased to 99% when the reaction was carried out at 100 °C (Table 1, entry 3). Using DMSO as the solvent also resulted in the same excellent yield (99%) (Table 1, entry 4). However, no product was observed in 1,4-dioxane, toluene and THF (Table 1, entries 5–7). Other bases, such as $K_2HPO_4 \cdot 3H_2O$, $KHCO_3$, K_2CO_3, Na_2CO_3, $NaHCO_3$, pyridine, Cs_2CO_3, NaOH, KOH, and NaOEt did not favour this transformation (Table 1, entries 8–17). Without CH_2Cl_2, the reaction did not proceed (Table 1, entry 18). When carried out in a sealed tube with 0.25 mL of CH_2Cl_2, the product was observed in 5% yield. When the temperature was increased to 125 °C, the reaction produced the product in 92% yield after 15 h. Similarly, **2a** was obtained in 71% yield when the system was charged with 0.1 mL CH_2Cl_2.

Table 1 Screening of the various reaction parameters for the condensation of salicylic acid (**1a**) and CH_2Cl_2[a]



1a **2a**

entry	Base	Solvent	*t* (h)	*T* (°C)	Yield[b] %
1	$K_3PO_4 \cdot 3H_2O$	DMF	6	60	Trace
2	$K_3PO_4 \cdot 3H_2O$	DMF	6	80	10
3	$K_3PO_4 \cdot 3H_2O$	DMF	6	100	99
4	$K_3PO_4 \cdot 3H_2O$	DMSO	6	100	99
5	$K_3PO_4 \cdot 3H_2O$	1,4-Dioxane	6	100	NR
6	$K_3PO_4 \cdot 3H_2O$	Toluene	6	100	NR
7	$K_3PO_4 \cdot 3H_2O$	THF	6	100	NR
8	$K_2HPO_4 \cdot 3H_2O$	DMF	6	100	15
9	$KHCO_3$	DMF	6	100	NR
10	K_2CO_3	DMF	6	100	Trace
11	Na_2CO_3	DMF	6	100	NR
12	$NaHCO_3$	DMF	6	100	NR
13	Pyridine	DMF	6	100	NR
14	Cs_2CO_3	DMF	6	100	Trace
15	NaOH	DMF	6	100	Trace
16	KOH	DMF	6	100	Trace
17	NaOEt	DMF	6	100	10
18[c]	$K_3PO_4 \cdot 3H_2O$	DMF	6	100	NR
19[d]	$K_3PO_4 \cdot 3H_2O$	DMF	6	100	<5
20[e]	$K_3PO_4 \cdot 3H_2O$	DMF	15	125	92
21[f]	$K_3PO_4 \cdot 3H_2O$	DMF	15	125	71

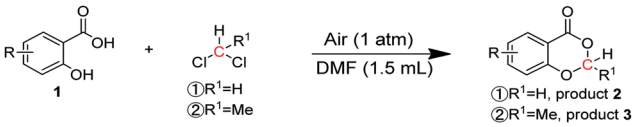
[a] Reaction conditions: salicylic acid (0.5 mmol), bases (1 mmol), CH_2Cl_2 (0.6 mL), solvent (1.5 mL). [b] Isolated yield based on **1a**, NR = no reaction. [c] The reaction was carried out with no CH_2Cl_2. [d] CH_2Cl_2 (0.25 mL), sealed tube. [e] CH_2Cl_2 (0.25 mL), sealed tube. [f] CH_2Cl_2 (0.1 mL), sealed tube.

With the optimal reaction conditions in hand, various salicylic acids **1** were screened. The results are summarized in Table 2. Various groups substituted on the benzene ring, such as methyl, fluoro, chloro, bromo, methoxy, trifluoromethyl, amino and *tert*-butyl, were tolerated well under the standard reaction conditions and gave excellent yields (Table 2, entries 1–13). Based on this series of experiments, substituents at the *ortho*-, *meta*-, and *para*-positions of the aromatic moiety did not significantly affect the outcome (Table 2, entries 2–13), especially noticing the high reactivity of **1q**, with two bulky *tert*-butyl groups (Table 2, entry 17). Meanwhile, both the electron-rich (Table 2, entries 2–4, entries 11–13, entries 15 and 17) and electron-deficient salicylic acids (Table 2, entries 5–10, entries 14 and 16) gave excellent yields. The trifluoromethyl group, a significant group in the life sciences,[33] as well as the unprotected amino group, could be tolerated in this transformation very well (Table 2, entries 14 and 15), affording the desirable products in 75% and 90% yields, respectively. Notably, the halogen groups could survive well under the standard reaction conditions and no cleavage of the C–halogen bond was observed (Table 1, entries 5–10). Salicylic acid with two chlorine groups could also furnish the desired product in 70% yield (Table 2, entry 16). These products with halogen groups could be applied for further functionalization to build useful and more complicated molecules.

The above results inspired us to further demonstrate the application of our developed protocol into coupling of salicylic acids with $CHCl_2CH_3$ for the synthesis of 2-methyl-substituted 4*H*-benzo[*d*][1,3]dioxin-4-ones, as depicted in Table 2 as well as in S3 in ESI,† for screening the reaction conditions. **1a** could be smoothly transformed into the desired products in 65% yield (Table 2, entry 18). Either electron-donating groups or electron-withdrawing groups at the aromatic rings of the salicylic acids were well tolerated, such as Me, OMe, F, Cl, $(CH_3)_3C$ (Table 2, entries 19–25). The steric hindrance of the substituted groups had a slight effect on the transformation. *Ortho*-substituted salicylic acids were converted to the desired products in relatively lower yields, compared to the ones substituted at the *meta*- or *para*-positions (Table 2, entry 19 *vs.* 20 and entry 23 *vs.* 24). Substituted salicylic acid **1q** with two *tert*-butyl groups could provide the desired product in 52% yield (Table 2, entry 25). In summary, salicylic acid bearing electron-donating groups (methyl, methoxy) and halogen groups (fluoro, chloro) did not give conspicuous differences in yields, and steric hindrance may have a slight impact on the reaction. The overall yields of $CHCl_2CH_3$ are lower than CH_2Cl_2 as a starting material, which may be due to $CHCl_2CH_3$ being more crowded than dichloromethane.

The reaction was successfully performed on a larger scale to demonstrate the practicability of this methodology. Products **2a** and **2n** could be conveniently obtained on a 15 mmol scale in yields similar to those on a small scale (*e.g.*, **2a:** 99% *vs.* 98% and **2n:** 98% *vs.* 98%) (see S4 and S5 in ESI†).

Table 2 Syntheses of products 2[a] and 3[b]



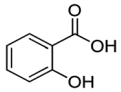
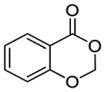
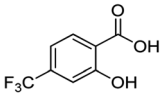
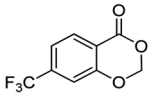
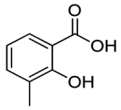
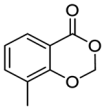
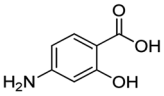
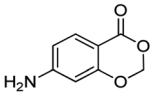
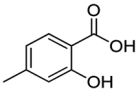
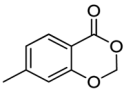
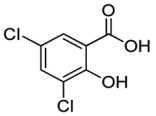
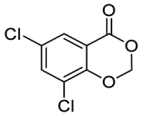
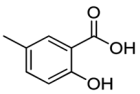
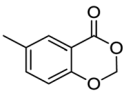
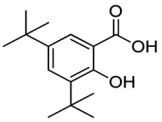
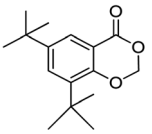
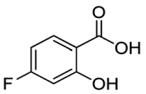
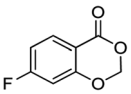
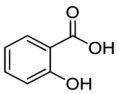
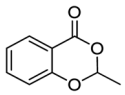
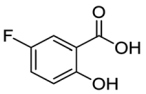
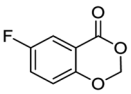
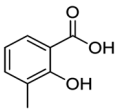
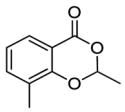
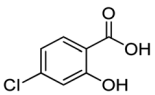
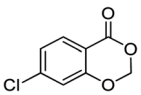
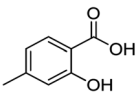
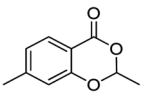
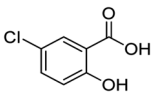
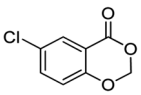
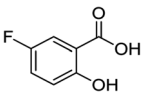
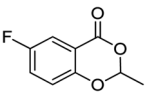
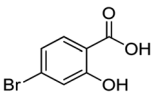
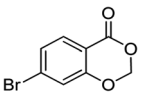
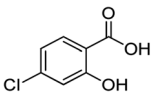
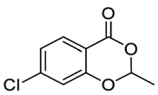
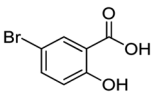
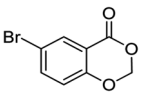
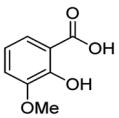
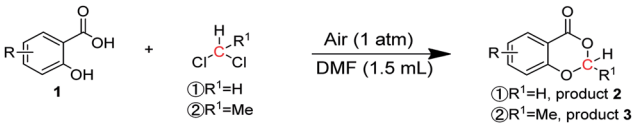
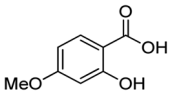
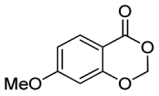
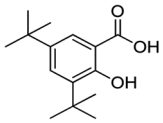
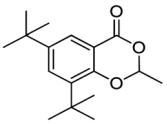
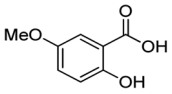
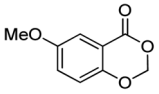
Entry	1		Product	Yield[c]	Entry	1		Product	Yield[c]
1		**1a**		**2a** (>99%)	14[d]		**1n**		**2n** (75%)
2		**1b**		**2b** (99%)	15		**1o**		**2o** (90%)
3		**1c**		**2c** (99%)	16[e]		**1p**		**2p** (70%)
4		**1d**		**2d** (98%)	17		**1q**		**2q** (98%)
5		**1e**		**2e** (97%)	18		**1a**		**3a** (65%)
6		**1f**		**2f** (89%)	19		**1b**		**3b** (49%)
7		**1g**		**2g** (95%)	20		**1c**		**3c** (53%)
8		**1h**		**2h** (96%)	21		**1f**		**3f** (55%)
9		**1i**		**2i** (90%)	22		**1g**		**3g** (43%)
10		**1j**		**2j** (92%)	23		**1k**		**3k** (43%)
11		**1k**		**2k** (98%)	24		**1m**		**3m** (51%)

Table 2 (*Contd.*)



Entry	1	Product	Yield[c]	Entry	1	Product	Yield[c]
12	 **1l**		**2l** (99%)	25	 **1q**		**3q** (52%)
13	 **1m**		**2m** (95%)				

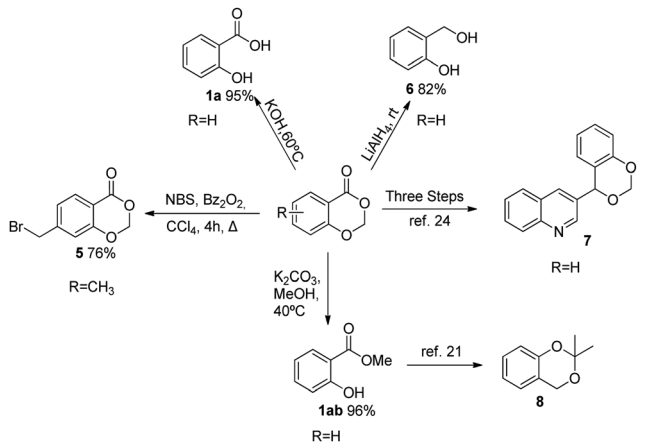
[a] Reaction conditions: **1** (0.5 mmol), $K_3PO_4 \cdot 3H_2O$ (1 mmol), CH_2Cl_2 (0.6 mL), DMF (1.5 mL), 6 h, 100 °C. [b] Reaction conditions: **1** (0.5 mmol), $K_3PO_4 \cdot 3H_2O$ (1 mmol), CH_3CHCl_2 (0.6 mL), DMF (1.5 mL), 10 h, 130 °C. [c] Isolated yields based on **1**. [d] 6 h. [e] 8 h.

4*H*-Benzo[*d*][1,3]dioxin-4-ones are versatile building blocks in organic synthesis. After this cyclization protocol was established, we looked forward to applying these cyclic products to further transformations (Scheme 2). For the classical hydrolysis reaction, **2a** was treated with stoichiometric 48% aqueous KOH, affording the corresponding salicylic acid in 95% yield.[22] When **2a** was treated with 10 mol% K_2CO_3 in MeOH, methyl salicylate **1ab** was produced in 96% yield. Furthermore, Itaru Sato and co-workers reported that **5** could be successfully converted to **8**.[21] 7-(Bromomethyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (**5**) could be obtained through the reaction of 7-(methyl)-4*H*-benzo[*d*][1,3]-dioxin-4-one (**2c**) with *N*-bromosuccinimide (NBS) in the presence of catalytic amounts of benzoyl peroxide (Bz_2O_2).[5] Upon treatment of **2a** with 4 equiv. of $LiAlH_4$, an 82% yield of 2-(hydroxymethyl)phenol (**6**) was produced.[20] **2a** can also undergo other transformations. For instance, compound **7**, a potential ingredient of insecticides, could be prepared using **2a** as the starting material,[24] thus has the potential to replace its analogues to finish their relative reactions.[1–23]

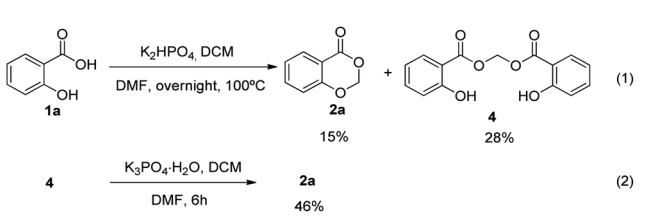
Consequently, some controlled experiments were carried out for understanding the reaction mechanism (Scheme 3). If 1 equiv. of $K_2HPO_4 \cdot 3H_2O$ participated in the reaction with CH_2Cl_2, **4** was the major product in 28% yield, as well as **2a** in 15% yield (eqn (1)). Increasing the amount of $K_2HPO_4 \cdot 3H_2O$ to 2 equiv., the yield of **2a** increased to 29%, while **4** was afforded in only 15%. When **4** reacted with CH_2Cl_2 under standard conditions for 6 h, **2a** was obtained in 46% yield (eqn (2)). Prolonging the reaction time to 12 h, **4** furnished **2a** in 71% yield. Surprisingly, **2a** could not be detected without CH_2Cl_2, indicating that CH_2Cl_2 might be involved in the procedure of intramolecular attack. In addition, **4** was not observed when employing $K_3PO_4 \cdot 3H_2O$ as the base in the course of the reaction.

On the basis of the results obtained, a plausible reaction mechanism was proposed and illustrated in Scheme 4. Initially, dehydration of salicylic acid (**1a**) formed a salt.[32] Subsequently, **A** reacted with CH_2Cl_2, providing product **2a** directly (Scheme 4).

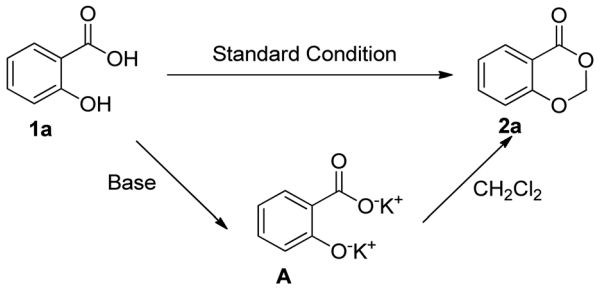
In conclusion, we have developed a practical and efficient method to construct 4*H*-benzo[*d*][1,3]dioxin-4-one and its derivatives, which are important structural units in insecticides, and intermediates to synthesize multiple-substituted benzene. The catalyst- and additive-free conditions, commercial and cheap starting materials and short reaction time, make this transformation pretty green, practical and attractive. Further studies on the reaction mechanism and the synthetic applications are ongoing in our laboratory.



Scheme 2 Transformations of 4*H*-benzo[*d*][1,3]dioxin-4-one.



Scheme 3 Controlled experiments.



Scheme 4 Proposed reaction mechanism.

Acknowledgements

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