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

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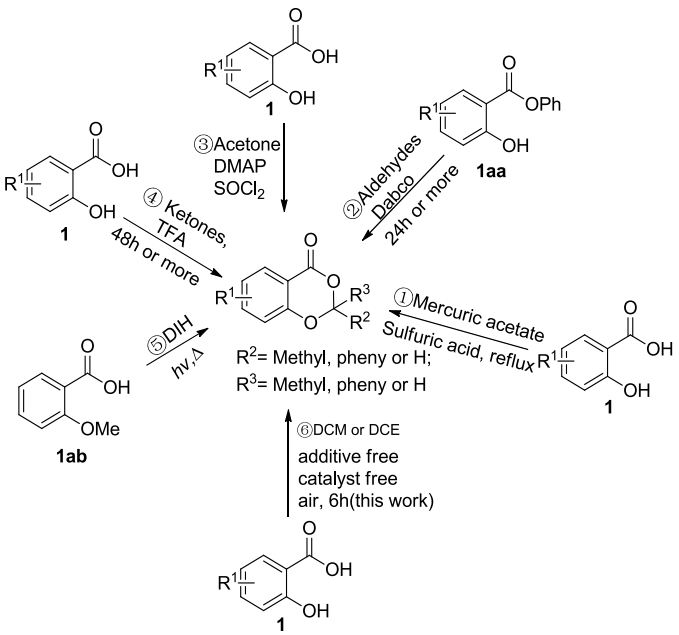
We have developed a green and practical method to construct 4*H*-benzo[*d*][1,3]dioxin-4-one and its derivatives, which are important structural units in insecticides, promising spice and intermediates to synthesize multiple-substituted benzene derivatives with great value. The catalyst- and additives-free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

Introduction

4*H*-Benzo[*d*][1,3]dioxin-4-one and its derivatives are of great promise for its wide applications in organic and pharmaceutical synthesis[1-23] as well as agriculture.[24] However, there exist few methodologies to build such a structure 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, Patrick 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 could be converted into 4*H*-benzo[*d*][1,3]-dioxin-4-ones by reacting with ketone, catalyzed by N,N-4-dimethylamino-prydine (DMAP) in the presence of stoichiometric $SOCl_2$ (③, Scheme 1)[8-19,28-29] and in the solution of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (④, Scheme 1).[5,20-22] Instead of TFA and trifluoroacetic anhydride, catalytic amount of sulfuric acid (H_2SO_4) and stoichiometric acetic anhydride could be used to prompt this transformation.[23] Gandelman and co-workers accidentally got the 4*H*-benzo[*d*][1,3]dioxin-4-one via irradiation of the mixture of *o*-methylsalicylic acid, 1,3-diiodo-5,5-dimehylhydantoin (DIH) and dichloroethane for 20h under refluxing (⑤, Scheme 1).[30]



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

However, some challenges still exit in these procedures, such as the unavailable starting materials, limitation of substrate scope, inevasible side reactions and requirement of strong acids. Therefore, a green, practical and efficient approach for 4*H*-benzo[*d*][1,3]dioxin-

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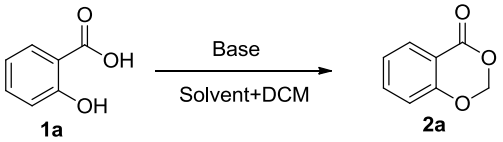
Table 1 Screening the various reaction parameters for the condensation of salicylic acid (**1a**) and CH_2Cl_2 [a]



1a 2a

Entry	Base	Solvent	t(h)	T(^{o}C)	Yield%[b]
1	$K_3PO_4.3H_2O$	DMF	6	60	Trace
2	$K_3PO_4.3H_2O$	DMF	6	80	10
3	$K_3PO_4.3H_2O$	DMF	6	100	99
4	$K_3PO_4.3H_2O$	DMSO	6	100	99
5	$K_3PO_4.3H_2O$	1,4-Dioxane	6	100	NR
6	$K_3PO_4.3H_2O$	Toluene	6	100	NR
7	$K_3PO_4.3H_2O$	THF	6	100	NR
8	$K_2HPO_4.3H_2O$	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]	$K_3PO_4.3H_2O$	DMF	6	100	NR
19[d]	$K_3PO_4.3H_2O$	DMF	6	100	<5
20[e]	$K_3PO_4.3H_2O$	DMF	15	125	92
21[g]	$K_3PO_4.3H_2O$	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. [g] CH_2Cl_2(0.1 mL), sealed tube.

-4-one and its derivatives from readily available starting materials are eagerly desirable. Herein, we present an unprecedented protocol to construct such a structure (⑥**,** Scheme 1). The significance of this methodology is: 1) CH_2Cl_2, a common and cheap reagent in laboratory, was seldom served as a reagent and C_1 source at the same time; [31-32] 2) additive and metal free reaction conditions; 3) moisture insensitivity and high efficiency.

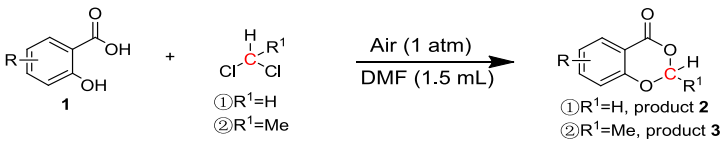
Results and Discussion

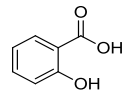
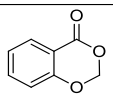
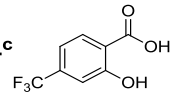
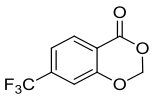
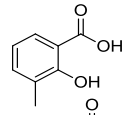
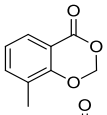
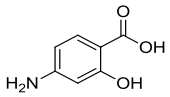
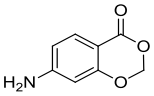
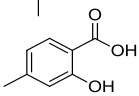
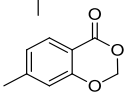
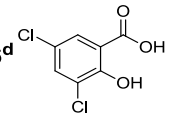
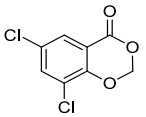
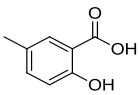
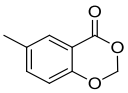
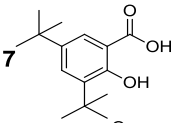
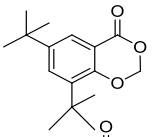
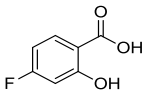
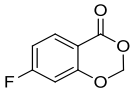
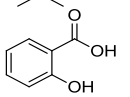
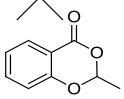
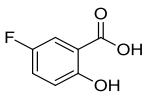
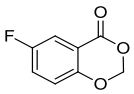
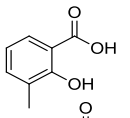
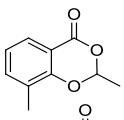
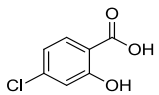
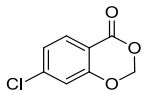
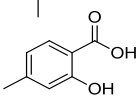
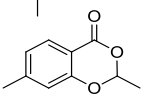
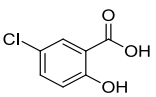
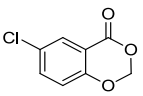
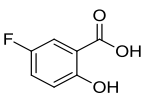
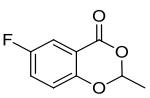
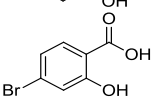
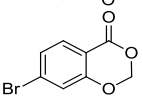
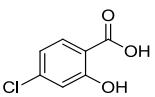
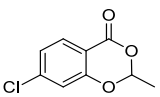
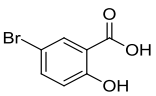
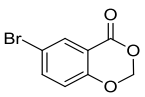
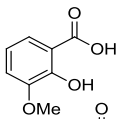
Initially, the reaction of salicylic acid (1a) with CH_2Cl_2 was chosen as a model reaction to screen the reaction parameters. K_3PO_4 $3H_2O$ was investigated firstly to screen the reaction temperature and solvent. Only a trace amount of the desired product was observed at 60 ^{o}C (Table 1, Entry 1). When temperature was raised to 80 ^{o}C, the desired product **2a** was achieved in 10% yield (Table 1, Entry 2). The yield could be increased to 99% when the reaction was carried out at 100 ^{o}C (Table 1, Entry 3). DMSO, as solvent, resulted in the same excellent yield (99%) as well (Table 1, Entry 4). However, no product was observed in 1,4-Dioxane, toluene and THF. (Table 1, Entry 5-7) Other bases, such as K_2HPO_4 $3H_2O$, $KHCO_3$, K_2CO_3, Na_2CO_3 and $NaHCO_3$, Pyridine, Cs_2CO_3, NaOH, KOH, NaOEt disfavoured this transformation (Table 1, Entry 8-17). Without CH_2Cl_2, the reaction did not proceed (Table 1, Entry 18). When carried out in sealed tube with 0.25 mL of CH_2Cl_2, the product was observed in 5% yield. Upgrading the temperature to 125 ^{o}C, the reaction provided the product in 92% yield after 15h. Similarly, **2a** was obtained in 71% yield when the system was charged with 0.1 mL CH_2Cl_2.

With the optimal reaction conditions in hand, various salicylic acids **1** were screened. The results were summarized in Table 2. Various substituted groups at benzene ring, such as methyl, fluoro, chloro, bromo, methoxy, trifluoromethyl, amino, 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 ortho-, meta-, and para-position of the aromatic moiety did not significantly affect the outcome (Table 2, Entries 2-4, Entries 5-6, Entries 7-8, Entries 9-10 and Entries 11-13), specially noticing the high reactivity of **1q**, with two bulky tert-butyl groups (Table 2, Entry 17). Meanwhile, both of electron-rich (Table 2, Entries 2-4, Entries 11-13, entry 15 and entry 17) and electron-deficient salicylic acids (Table 2, Entries 5-10, Entry 14 and Entry 16) could give excellent yields. Trifluoromethyl group, a significant group in life science[33] as well as the unprotected amino group could be tolerated in this transformation very well (Table 2, Entry 14 and Entry 15), affording the desirable products in 75% and 90% yields, respectively. Notably, 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 synthesis of 2-methyl-substituted 4***H***-benzo[*d*][1,3]dioxin-4-ones, as were depicted in Table 2 as well S3 in supporting information for screening reaction condition. **1a** could be smoothly transformed into the desired products in 65% yield (Table 2, Entry 18). Either electron-donating groups or electron-

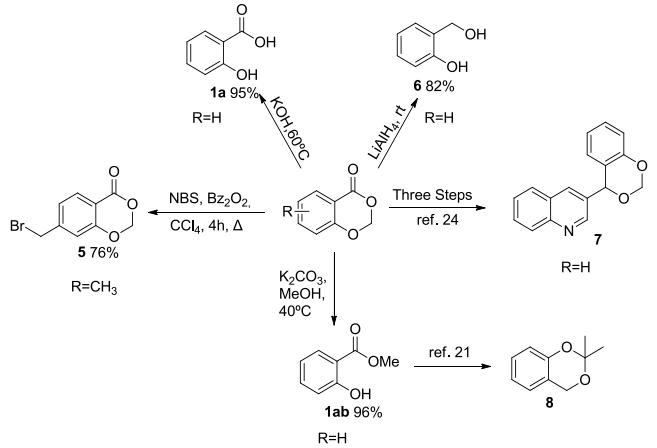
Table 2 Syntheses of the products **2**[a] and **3**[b]



Entry	1	Product	Yield[c]	Entry	1	Product	Yield[c]
1		1a		**2a**(>99%)	14[c]		1n		**2n**(75%)
2		1b		**2b**(99%)	15		1o		**2o**(90%)
3		1c		**2c**(99%)	16[d]		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%)
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 (1.5mL), 6h, 100ºC.
[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), 10h, 130ºC.
[c] Isolated yields based on **1** .[c]6h. [d]8h.

Scheme 3 Transformation of 4***H***-benzo[*d*][1,3]dioxin-4-one



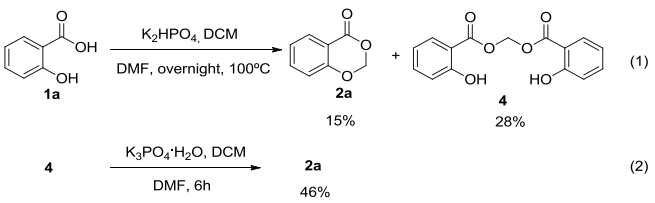
-withdrawing groups at the aromatic rings of salicylic acids were well tolerated, such as Me, OMe, F, Cl, $(CH_3)_3C$ (Table 2, Entries 19-25). The steric hindrance of substituted groups had slightly effect on the transformation. *Ortho*-substituted salicylic acids were converted to the desired products in relative lower yields, compared to the ones substituted at meta- or para- position (Table 2, Entries 19 *vs* 20 and Entries 23 *vs* 24). Substituted salicylic acid **1q** with two tert-butyl groups could provide the desired product in 52% yield (Table 2, Entry 25). Summarily, 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, maybe due to that $CHCl_2CH_3$ is more crowded than dichloromethane.

The reaction on a larger scale to demonstrate the practicability of this methodology was successfully performed. Products **2a** and **2n** could be conveniently obtained on 15 mmol scale in yields similar to those on a small scale (e.g., **2a**: 99% *vs* 98%; **2n**: 98% *vs* 98%, respectively) (See S4-5 in Supporting Information).

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 in further transformations (Scheme 3). 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 amount of benzoyl peroxide (Bz_2O_2).[5] Upon treatment of **2a** with 4 equiv of $LiAlH_4$, a 82% yield of 2-(hydroxymethyl)phenol (**6**) was provided.[20] **2a** could also undergo other transformations. For instance, compound **7**, a potential ingredient of insecticides, could be prepared using **2a** as the starting material,[24] thus potential to replace its analogues to finish their relative reactions.[1-23]

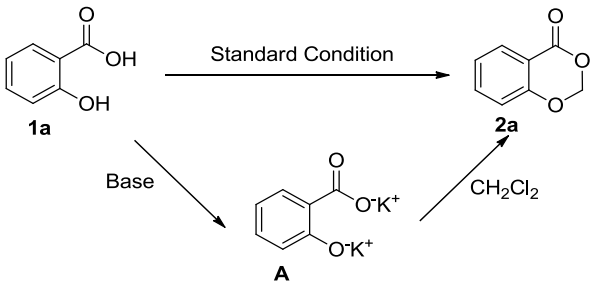
Consequently, some controlled experiments were carried out for understanding the reaction mechanism (Scheme 4). If 1 equiv of $K_2HPO_4\,3H_2O$ participated in the reaction with CH_2Cl_2, **4** was the major product in 28% yield, as well as **2a** in 15% yield (eq (1)). Increasing the amount of $K_2HPO_4\,3H_2O$ 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 condition for 6h, **2a** was obtained in 46% yield (eq (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 involve in the procedure of intramolecular attack. In addition, **4** was not observed, when employing $K_3PO_4\,3H_2O$ as base in the course of the reaction.

Scheme 4 Controlled Experiments



On the basis of the results obtained, a plausible reaction mechanism was proposed and illustrated in Scheme 5. Initially, dehydration of salicylic acid (**1a**) formed a salt.[32] Subsequently, **A** reacted with CH_2Cl_2, providing product **2a** directly (Scheme 5).

Scheme 5: Proposed Reaction Mechanism



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, promising spices 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 to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

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Metal-free and additive-free base-mediated formation of 4***H***-benzo[*d*][1,3]dioxin-4-one and its derivatives from salicylic acids and dichloromethane was developed, using dichloromethane (DCM) and 1,1-dichloroethane (1,1-DCE) as a C1 source.