



Kolbe–Schmitt type reaction under ambient conditions mediated by an organic base†

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The combined use of an organic base for resorcinols realized a Kolbe–Schmitt type reaction under ambient conditions. When resorcinols (3-hydroxyphenol derivatives) were treated with DBU under a carbon dioxide atmosphere, nucleophilic addition to carbon dioxide proceeded to afford the corresponding salicylic acid derivatives in high yields.

Aromatic carboxylic acids are one of the representative units capable of various chemical conversions. With their high demand in organic synthesis, the development of preparative methods for carboxylic acid derivatives has been studied extensively.¹ Among those methods, a nucleophilic carboxylation of a carbanion generated from the corresponding halobenzene precursor with carbon dioxide,² a benzylic C–H oxidation of toluene derivatives,³ or hydrolysis of benzonitrile derivatives,⁴ *etc.*,⁵ has been used to reach aromatic carboxylic acids for a long time. Almost all of those methods require toxic reagents to prepare the precursors, and/or an energy consumption process such as conducting at high temperatures. In contrast to the classical routes towards aromatic carboxylic acids, one of the most ideal and direct strategies for their synthesis is carboxylation of C–H bonds on the aromatics using carbon dioxide sources.⁶ Although C–H carboxylation has developed rapidly with the recent progress of C–H activation chemistry, the use of transition metal catalysts and harsh reaction conditions is inevitable in most cases. It is of great significance to work on the development of a transition metal-free approach for the conversion of aromatic C–H bonds in terms of green sustainable chemistry.

Utilization of carbon dioxide as the C1 source is actively studied because of its low toxicity, availability at low cost, and easy handling.⁷ Since carbon dioxide is thermodynamically stable and kinetically inert, generally harsh reaction conditions or strong nucleophiles were required for the carboxylation reaction. Therefore, the development of carbon dioxide fixation under mild reaction

conditions has been a challenge and is highly desirable. In particular, a carbon–carbon bond formation reaction of aromatics with carbon dioxide is very useful for the preparation of benzoic acid derivatives that can be used for various chemical transformations.

The Kolbe–Schmitt reaction is well known as a practical reaction to provide salicylic acid derivatives through carbon–carbon bond formation of sodium phenoxide with a carbon dioxide. Since the original report in the 19th century,⁸ much effort has been made for its improvement or modification; however, high-temperature and/or high-pressure conditions are still needed for sufficient conversion.⁹

Resorcinols (= 3-hydroxyphenols) are often applied for the Kolbe–Schmitt reaction to prepare the corresponding salicylic acids (resorcylic acids). For example, some of the bioactive compounds and their analogs such as tetrahydrocannabinol and platensimycin were synthesized *via* the Kolbe–Schmitt reaction on resorcinol derivatives, though the carboxylation steps often proceeded in low yields (Fig. 1).¹⁰ Nevertheless, there were other attempts to improve the Kolbe–Schmitt reaction on resorcinols, but harsh reaction conditions such as high temperature or quite high pressure (scCO₂) were still required.¹¹ Recently, Faber's and Zhu's groups reported that carbon dioxide fixation on resorcinols using enzymes provided the corresponding acids around room temperature in the presence of a carbon dioxide source but the method leaves an issue in the substrate scope.¹²

While the organic base-catalyzed carbon dioxide fixation reaction into aromatics has been intensively studied, there have been few reports for the reaction involving carbon–carbon bond formation of

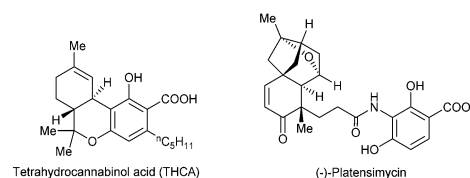


Fig. 1 Biologically active compounds synthesized by the Kolbe–Schmitt reaction on resorcinols.

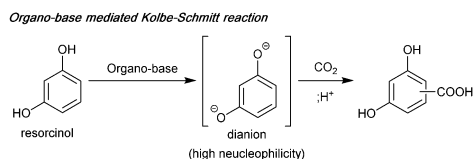
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aromatics with carbon dioxide.¹³ Skystrup and co-workers recently reported organic base-catalyzed incorporation of carbon dioxide into alkynyl indoles based on the formation of a CO₂-guanidine complex.^{14,15} Although this is the first example of organocatalyzed CO₂ fixation involving C-C and C-O bond formation and the reaction proceeds well with a small amount of carbon dioxide under atmospheric pressure, the reaction needs to be carried out at a high temperature (100 °C). Therefore, to achieve an organic base reaction involving carbon dioxide fixation under low temperature is not a trivial issue.

We envisioned that the dianion species derived from resorcinol would have a nucleophilicity high enough to promote the addition reaction to carbon dioxide being able to proceed efficiently. Resorcinol has relatively low pK_a, and the corresponding dianion could be generated easily by treatment of a strong organic base.¹⁶ In this paper, we report the Kolbe-Schmitt type reaction of resorcinols under ambient conditions using an organic base to synthesize the corresponding salicylic acids *via* the nucleophilic addition of phenolate and CO₂ (Scheme 1).

Various bases were screened for this Kolbe-Schmitt type reaction of resorcinol (**1a**) under 2.0 MPa of carbon dioxide at 30 °C for 24 hours (Table 1).¹⁷ Using NEt₃ (pK_a 18.8),¹⁸ the reaction did not proceed at all (entry 1). Next, when the reaction was carried out using guanidine bases TMG (pK_a 23.4), BTMG (pK_a 26.5), TBD (pK_a 26.0), and MTBD (pK_a 25.5), which are stronger bases than tertiary alkyl amines,



Scheme 1 Concept of this work.

Table 1 Examination of reaction conditions

Entry	Base	Solvent	Recovery 1a ^a /%	Yield 2a ^a /%
1	Et ₃ N	CH ₃ CN	Quant	nd
2	TMG	CH ₃ CN	9	87
3	BTMG	CH ₃ CN	nd	95
4	TBD	CH ₃ CN	25	70
5	MTBD	CH ₃ CN	nd	99
6	DBU	CH ₃ CN	nd	> 99 ^b
7	DBU	DMF	nd	> 99
8	DBU	Toluene	56	22

R = H: TMG
R = tBu: BTMG

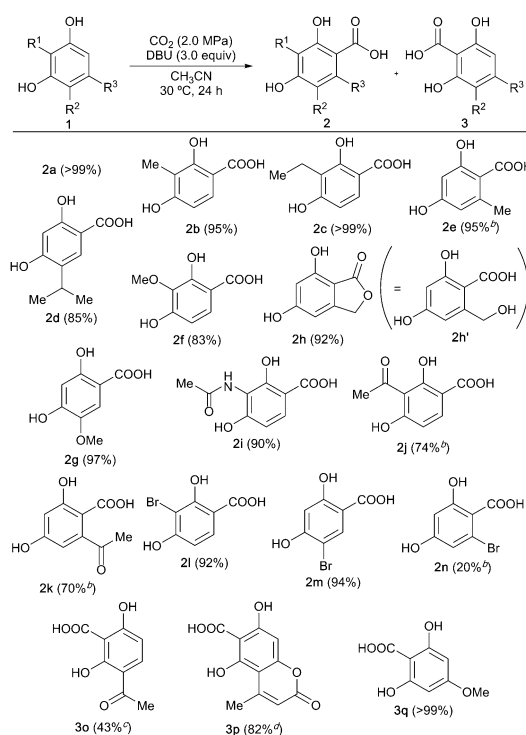
R = H: TBD
R = Me: MTBD

DBU

^a Yields were determined by ¹H NMR using 1,1,2,2-tetrachloroethane as internal standard. ^b Isolated yield. TMG = *N,N,N',N'*-tetramethylguanidine, BTMG = *tert*-butyltetramethylguanidine, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

yields of **2a** were remarkably improved to 70–95% (entries 2–5)¹⁸ (pK_a values of the corresponding conjugated acid in CH₃CN). These results might be due to the dianion species, which could be generated from the reaction of **1a** with a base. Finally, it was found that the use of DBU (= 1,8-diazabicyclo[5.4.0]undec-7-ene, pK_a 24.34) resulted in a quantitative formation of the desired product (entry 6),¹⁸ and DBU was defined as an optimum base in terms of yield and cost. The other solvents were used for this reaction with DBU. The product was also quantitatively obtained in DMF solvent (entry 7), whereas the use of toluene as a solvent caused a lower yield (entry 8).

The optimized reaction conditions were applied to various resorcinols (Scheme 2). The alkyl-substituted resorcinols were first examined (**1b–e**). The substrates containing a methyl or an ethyl group on R¹ were converted to the corresponding salicylic acids (**2b** and **2c**) in 95% and >99% yields, respectively. When the substrate bearing an isopropyl group on R² was employed, the desired product **2d** was obtained in 85% yield. When the substrate having a methyl group on R³ was examined, the reaction proceeded to afford the corresponding product **2e** in 95% yield. The resorcinols substituted by electron-donating groups were next examined (**1f–i**). The substitution of a methoxy group on R¹ or R² resulted in the formation of the desired salicylic acids (**2f** and **2g**) in 79% and 97% yields, respectively. The substrate bearing a hydroxymethyl group on R³ was converted to the product **2h** (= 5,7-dihydroxyphthalide) *via* the corresponding salicylic acid **2h'** after quenching of the reaction with 1 M aqueous solution of HCl. When the substrate having an acetamide group as R¹ was employed, the reaction proceeded to afford the corresponding product **2i** in 90% yield, which is a structural motif of platensimycin.¹⁰ Resorcinols substituted by



Scheme 2 Scope of DBU-mediated Kolbe-Schmitt reaction.^a ^aIsolated yields. ^b40 °C. ^c100 °C, DMF, 48 h. ^d50 °C.

electron-withdrawing groups were examined (**2j–n**). The substrates containing an acetyl group as R¹ and R³ were converted into the corresponding salicylic acids (**2j** and **2k**) in 79% and 70% yields, respectively. The substitution of a bromo group as R¹, R², and R³ resulted in the formation of the desired products (**2l–n**) in 92%, 94%, and 20% yields, respectively. It was found that the product **2n** was unstable under the reaction conditions and the reverse reaction proceeded considerably,¹⁹ which might be the reason for the low yield of **2n**. A different site-selectivity of the carboxylation was observed when the substrates **1o–1q** were employed for this reaction. The substrate **1o** bearing an acetyl group on R² was employed at 100 °C to afford the salicylic acid **3o** in 43% yield. Resorcinol **1p** having a coumarin scaffold on R² and R³ was treated in the reaction at 50 °C to afford the product **3p** in 82% yield. The substitution of a methoxy group on R³ resulted in the formation of the salicylic acid **3q** in a quantitative yield.²⁰

According to the literature, it is reasonable to consider that the corresponding dianion species were generated from resorcinols with a treatment of an excess amount of DBU.¹⁶ When 1 equivalent of DBU was added to CD₃CN solution of **1a** under nitrogen atmosphere, the resolution of the peaks decreased because of the formation of an insoluble material in the NMR tube and all peaks were observed to shift toward a higher magnetic field by the formation of an anion intermediate. Then, the H_b peak was observed in the highest magnetic field (Fig. 2(b)) while H_a was in the highest magnetic field without DBU (Fig. 2(a)). Importantly, such a characteristic peak shift of H_a and H_b was not observed in the case of NEt₃. Next, by adding 2 equivalents of DBU, the insoluble material was dissolved, and all peaks further shifted toward a higher magnetic field involving recovery of high peak resolution. With more than 3 equivalents of DBU, the peak shift was no longer observed, suggesting the formation of a dianion intermediate (Fig. 2(c)). Carbon dioxide is selectively trapped on C_b and the high distribution of electron density on C_b in the HOMO orbitals of the dianion state of **1a** is confirmed by theoretical calculation.²¹ On the other hand, when the same experiment was carried out using **1o**, which was carboxylated at C_a, H_a existed in the highest magnetic field even after the addition of

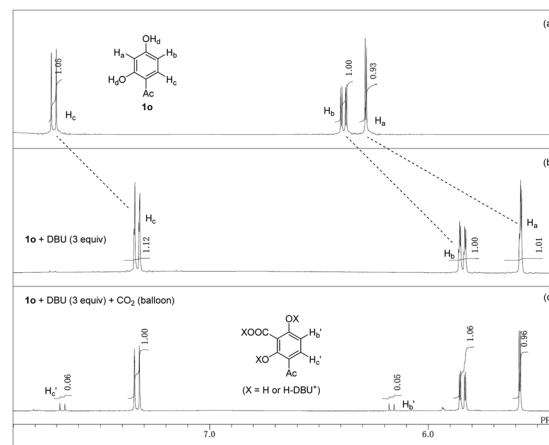


Fig. 3 NMR spectra of **1o** with DBU and carbon dioxide.

3 equivalents of DBU (Fig. 3(b)). Therefore, C_a should be the most reactive site on **1o** and the nucleophilicity of C_a is also supported by the theoretical calculation of the HOMO orbitals of the dianion of **1o**.

The DBU-mediated Kolbe–Schmitt type reaction under practical conditions was examined (Scheme 3). It was confirmed that carboxylation of **1a** proceeded well to afford **2a** in >99% yield at 30 °C under balloon pressure of carbon dioxide.²² Alkyl group substituted resorcinols **1b** and **1c** were also converted into the corresponding resorcylic acids **2b** and **2c** with high efficiency. Resorcinols **1d** and **1e** bearing methoxy groups were employed under similar conditions to furnish **2d** and **2e** in good yields.²³ To further test the flexibility of this methodology, it was investigated whether it could be applied to a preparative-scale synthesis. When the carboxylation of **1a** (11.1 g, 100 mmol) was carried out under more easily accessible conditions than the optimized ones (balloon pressure of CO₂ at room temperature), **2a** was obtained in 84% yield (12.9 g, 83.8 mmol) without purification by silica-gel column chromatography.

In conclusion, we have developed a DBU-mediated Kolbe–Schmitt type reaction for resorcinols under ambient conditions.

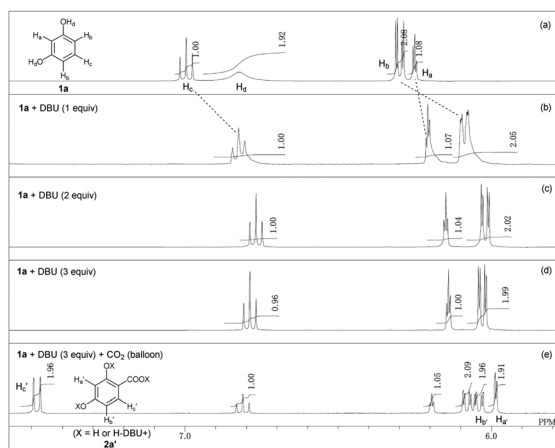
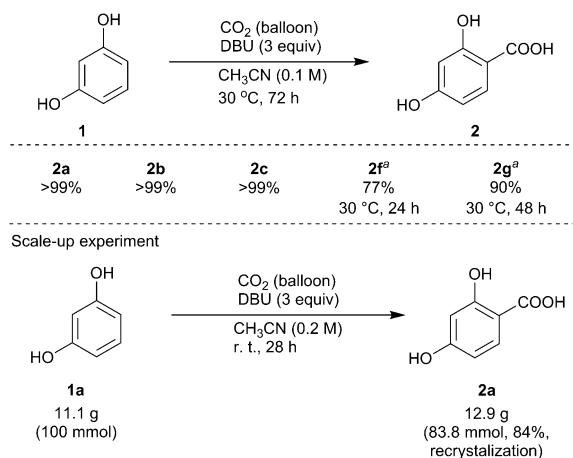


Fig. 2 NMR spectra of **1a** with DBU and carbon dioxide.



Scheme 3 Scope of DBU-mediated Kolbe–Schmitt type reaction operated in a round-bottom flask and scale-up synthesis. ^aMS 3A (100 mg) was used.

The corresponding salicylic acids were successfully derived from resorcinols in high yields. The site-selectivity of carboxylation was clearly controlled by the substituents on resorcinol, and the product was obtained as a single isomer in all cases. The reactive intermediate and the site-selectivity were elucidated by NMR experiments, mainly. It was demonstrated that this methodology could be applicable for a preparative-scale synthesis under atmospheric pressure of carbon dioxide around room temperature.

Conflicts of interest

The authors declare no conflict of interest.

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- 19 See ESI† for more detailed discussion.
- 20 **3q** is a thermodynamic product. See ESI† for more detailed study on the selectivity of carboxylation.
- 21 See ESI†.
- 22 The pressure of the CO₂ balloon was measured by a pressure gauge, and it showed that the pressure was below 1.1 atm.
- 23 Resorcinols bearing electron withdrawing groups were not efficiently converted into carboxylated products under atmospheric pressure of carbon dioxide.