

Computer-Assisted Design of Ionic Liquids for Efficient Synthesis of 3(2H)-Furanones: A Domino Reaction Triggered by CO₂

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S Supporting Information

ABSTRACT: A strategy for the highly efficient synthesis of 3(2H)-furanones by hydration of diyne alcohols catalyzed by base-functionalized ionic liquids under atmospheric-pressure CO₂ that was developed through computer-assisted design is reported. The best range of basic ionic liquids as catalysts was predicted at first, and [HDBU][BenIm] exhibited the highest catalytic activity. Through a combination of NMR spectroscopic investigations and quantum-chemical calculations, the results indicated the importance of the basicity of the anion and the species of cation in the ionic liquid.

Considerable attention has been drawn to CO₂ capture and utilization (CCU), as CO₂ is the main reason leading to climate change. On one hand, CO₂, an abundant and nontoxic C1 resource, has been converted into fuels and various useful chemicals, like urea, cyclic carbonates, and oxazolidinones.¹ On the other hand, CO₂ can be utilized to tune the physical properties of liquids or be a cocatalyst that is effective and accessible.² A CCU process under mild conditions is still challenging because CO₂ is at the most oxidized state of carbon and is thermodynamically stabilized. Ionic liquids (ILs) exhibit outstanding performance in CO₂ capture because of their unique properties.³ Recently, it was also discovered that many CCU processes (CO₂ acting as reactant or cocatalyst) can perform well under atmospheric-pressure CO₂ by tuning the properties of ILs. The ILs act both as absorbents and as activators in these reactions.⁴

3(2H)-Furanones are fundamental structural elements in many natural products, some of which exhibit antitumor, antibiotic, and antiulcer activities.⁵ Thus, effective strategies for their synthesis need to be developed. Acid-catalyzed cyclization–dehydration of 1-hydroxy-2,4-diketones is one of the traditional methods.⁶ What's more, transition metal catalysts, like Au, Ag, Cu, Pd, Pt, and Hg, and base-catalyzed cyclization were developed to afford 3(2H)-furanones.^{2h,i,7} However, these approaches usually require an excess of strong acid or base, volatile organic solvents, tedious processes for purification, and metal catalysts that are of poor reusability. Therefore, a challenging approach is to develop a novel method for the efficient synthesis of 3(2H)-furanones that is metal- and solvent-free.

Base-catalyzed reactions, such as the aldol reaction, Morita–Baylis–Hillman reaction, and Rauhut–Currier reaction, are important strategies to afford various natural products and

pharmaceuticals.⁸ Obviously, the basicity of the catalyst plays a significant role in these reactions: weak basicity results in low catalytic activity, while strong basicity leads to side reactions.⁹ However, the choice of basic catalyst is often based on experience and experimental trial and error. Therefore, a strategy that can predict the best range of basicities before experiment will have a profound influence in this field.

Herein we demonstrate a new method for the highly efficient synthesis of 3(2H)-furanones from diyne alcohols through a one-pot domino hydration reaction triggered by atmospheric-pressure CO₂. Through quantum-chemical calculations, a proper range of basicities was designed and predicted at first, and [HDBU][BenIm] was found to be very effective in this reaction during experiments, in good agreement with the prediction. The roles of the anion and the cation were also investigated through a combination of density functional theory (DFT) and NMR methods.

In a base-catalyzed reaction, can we select one of the most effective ILs before the experiment by simply using DFT calculations? One of criteria that represent basicity is the pK_a value. We wonder whether the catalytic activity can be evaluated just by comparing the pK_a values of the raw material and ILs.

The hydration of 2-methyl-6-phenylhexa-3,5-diyne-2-ol (**1a**) was selected as the model reaction to investigate the effect of different bases. At first, the pK_a value of **1a** was calculated,¹⁰ and the pK_a values (Figure 1) of various common anions (Figure 2) were obtained from previous works.¹¹ However, **1a** exhibited stronger basicity than Im, which was considered as a strong base, where the pK_a values were 20.5 and 14.2,

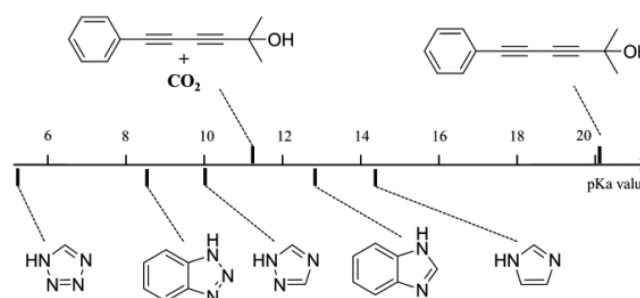


Figure 1. pK_a values of the complex of **1a** and CO₂, **1a**, and various azoles.

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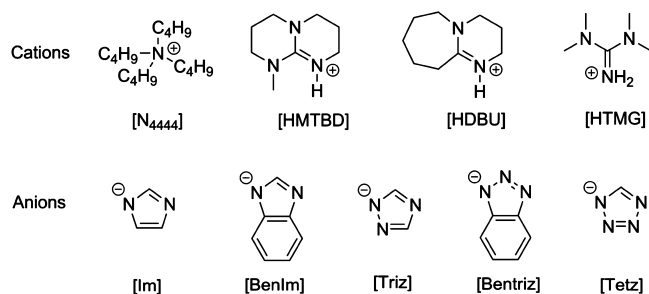


Figure 2. Structures of cations and anions used in this work.

respectively. It was reported that CO₂ can facilitate hydrogen abstraction.^{2b,4e} Therefore, CO₂ was taken into consideration in calculating the pK_a value of **1a**. Interestingly, this value declined to 11.2, which is between those of BenIm and Triz. Did this mean that BenIm or Triz anions would show higher catalytic reactivity than other anions?

To verify this hypothesis, the hydration of **1a** was carried out at 90 °C under CO₂ at atmospheric pressure (balloon). As shown in Table 1, when [N₄₄₄₄][Im] was used as the base, **1a**

Table 1. Effect of Different Basic Ionic Liquids on the Synthesis of 3(2H)-Furanones^a

entry	base	T (°C)	t (h)	yield (%) ^b
1	[N ₄₄₄₄][Im]	90	1	61
2	[N ₄₄₄₄][BenIm]	90	1	72
3	[N ₄₄₄₄][Triz]	90	1	70
4	[N ₄₄₄₄][Bentriz]	90	1	60
5	[N ₄₄₄₄][Tetz]	90	1	12
6	[HMTBD][BenIm]	90	1	72
7	[HDBU][BenIm]	90	1	84
8	[HTMG][BenIm]	90	1	47
9 ^c	[HDBU][BenIm]	90	1	<1
10	–	90	1	<1
11	Et ₃ N	90	1	<1
12	DBU	90	1	65
13	NaOH	90	1	<1
14	NaTriz	90	1	<1
15 ^d	Na ₂ CO ₃	90	1	<1
16	[HDBU][BenIm]	80	2	92

^aReaction conditions: **1a** (0.6 mmol), H₂O (6 mmol), base (0.6 mmol), and CO₂ (~1 bar, balloon). ^bDetermined by GC using an internal standard. ^cWithout CO₂. ^d0.3 mmol of Na₂CO₃ was added.

was converted completely and a 61% yield of **2a** was obtained. On the contrary, only a little bit of **1a** was converted when a weaker base IL, [N₄₄₄₄][Tetz], was used, while higher yields of **2a** were obtained when the moderately basic ILs [N₄₄₄₄][BenIm] and [N₄₄₄₄][Triz] were used (72 and 70%, respectively). Clearly, it worked out to be consistent with our prediction.

With [BenIm] as the anion, we also investigated the catalytic activity of many superbase-derived protic ILs (PILs). The basicity of these superbases could be ordered as MTBD > DBU > TMG. When [HMTBD][BenIm] and [HTMG][BenIm] were applied in this reaction, **2a** was obtained in 72 and 47%

yield, respectively. With moderate basicity, to our delight, [HDBU][BenIm] improved the yield of **2a** to 84%. The control experiments without CO₂ (Table 1, entry 9) or without base (entry 10) revealed that CO₂ and the base are essential to this reaction. This reaction did not proceed when Et₃N was used as the catalyst (entry 11), indicating the importance of the basicity of the base catalyst. Furthermore, the traditional superbase DBU could only give a moderate yield (entry 12). The use of traditional inorganic bases such as NaOH, NaTriz, and Na₂CO₃ did not promote the reaction (entries 13–15). This poor catalytic activity should be ascribed to their poor CO₂ activation. After screening of the reaction conditions (Table S1), the yield of **2a** improved to 92% when the reaction was performed at 80 °C for 2 h (entry 16).

Clearly, [BenIm] is a suitable anion in this reaction on the basis of either the DFT prediction or the experimental results. However, why does the cation of the IL have such a significant effect on this reaction, with superbase-derived protic ILs normally exhibiting higher catalytic activity than aprotic ILs?

To begin with, the basicities of these ILs should be taken into account, since this reaction is sensitive to the basicity of the catalyst. Therefore, NMR spectroscopic experiments were utilized to compare their basicities (Figure 3). When the H

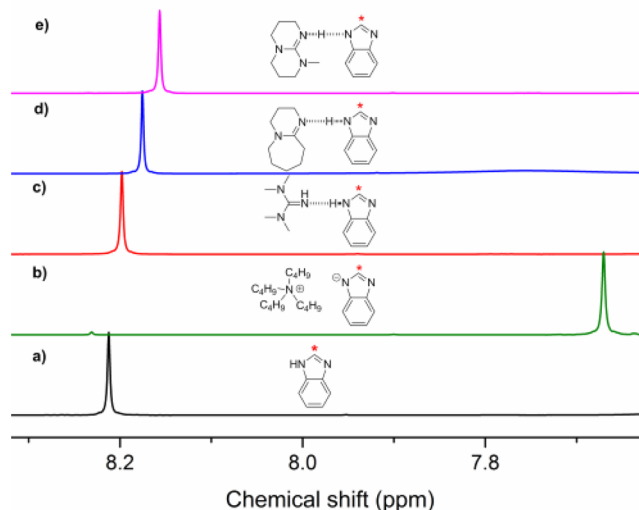


Figure 3. ¹H spectra of (a) BenIm, (b) [N₄₄₄₄][BenIm], (c) [HTMG][BenIm], (d) [HDBU][BenIm], and (e) [HMTBD][BenIm].

in BenIm was abstracted, the H signal of C2–H moved from 8.22 to 7.67 ppm (Figure 3a,b). Surprisingly, that signal just moved less than 0.1 ppm in these three superbase-derived protic ILs. For example, that signal was at 8.21 and 8.18 ppm in [HTMG][BenIm] and [HDBU][BenIm], respectively (Figure 3c,d). As for [HMTBD][BenIm], where the cation had the strongest basicity in these protic ILs, the H signal of C2–H moved only 0.06 ppm, to 8.16 ppm (Figure 3e). Clearly, these PILs mainly existed in the state of molecular pairs rather than ion pairs, as mainly appeared in [N₄₄₄₄][BenIm]. Moreover, the natural bond orbital (NBO) charges of these ILs were also calculated (Table S2). It was found that the NBO charge on N varied from –0.583 to –0.580 in these PILs, which is lower than that in [N₄₄₄₄][BenIm] (–0.644). Accordingly, the basicities of these PILs are lower than that of [N₄₄₄₄][BenIm].

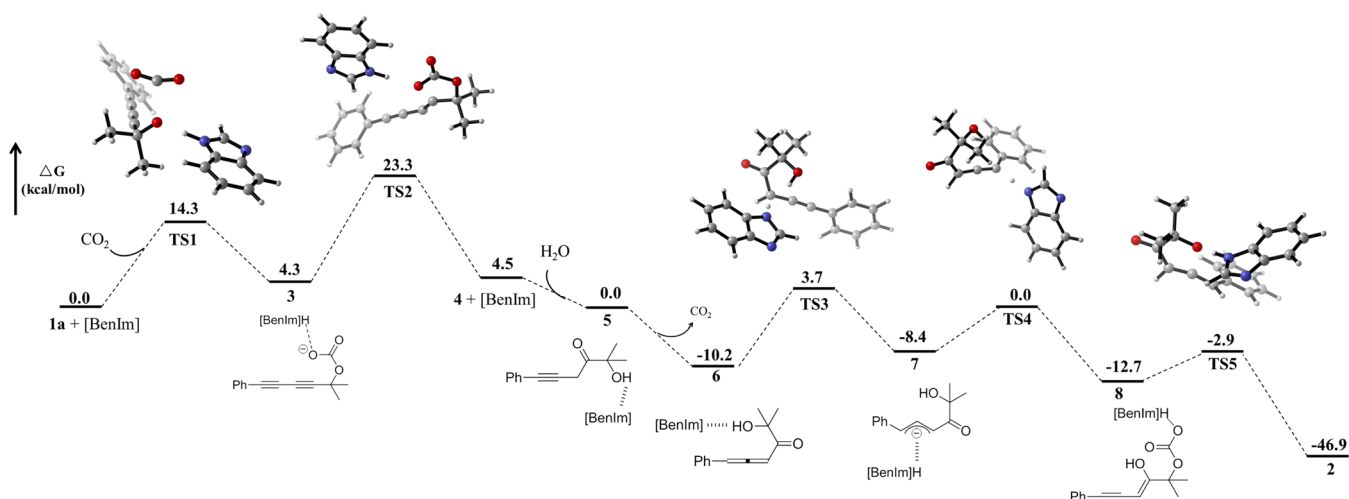


Figure 4. Computational studies of the reaction mechanism.

Therefore, the appropriate basicity of [HDBU][BenIm] should be one of the reasons for its high catalytic activity.

Subsequently, the mechanism of this domino reaction was investigated by DFT calculations (Figures 4 and S1).¹⁰ At first, **1a** reacts with CO₂ in the presence of [BenIm], overcoming an energy barrier of 14.3 kcal/mol. Then, the intramolecular cyclization of **3** requires an activation free energy of 23.3 kcal/mol, making it the rate-determining step in this reaction. The cyclic carbonate **4** is hydrolyzed and releases CO₂ to afford **6** under the base [BenIm]. Finally, **8** is formed through isomerization of **6** with the base catalyst, and intramolecular cyclization of **8** affords the product **2a**.

Therefore, the intramolecular cyclization of **3** was picked up to investigate the difference between protic ILs and aprotic ILs in this reaction (Figure 5).¹² The energy barrier would be

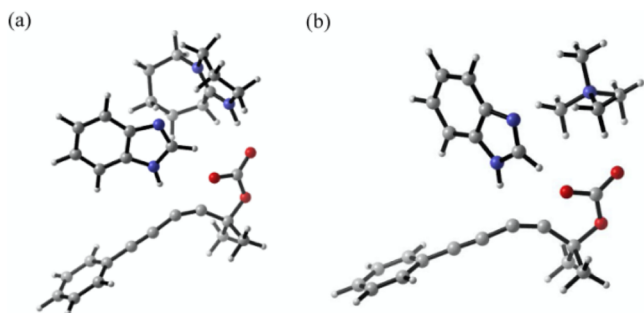


Figure 5. Structures of TS2 with (a) [HDBU][BenIm] ($\Delta G = 24.6$ kcal/mol) or (b) [N₁₁₁₁][BenIm] ($\Delta G = 25.6$ kcal/mol) as the base.

higher while considering cations; a similar phenomenon was also reported in SO₂ absorption.¹³ The energy demand for the cyclization process with [HDBU][BenIm] was 24.6 kcal/mol, while it was 25.6 kcal/mol with [N₁₁₁₁][BenIm] as the base. Interestingly, the basicity of [N₁₁₁₁][BenIm] should be stronger than that of [HDBU][BenIm] (Figure 3). At this point, the NBO charges of **3** with different catalysts were also calculated. As shown in Figure S2, the NBO charges of C and O were 0.126 and -0.799, respectively, with [BenIm] as the base. When the cations were taken into consideration, these differences were much smaller. When [HDBU][BenIm] was used, the difference in the NBO charges of C and O was 0.861, while it was 0.855 with [N₁₁₁₁][BenIm] as the catalyst. Clearly,

the larger difference in NBO charges, the easier this reaction would proceed.

With the optimized conditions in hand, the utility and generality of this reaction was also investigated (Table 2). First,

Table 2. Substrate Scope of the [HDBU][BenIm]-Catalyzed Domino Reaction^a

entry	substrate	R ¹	R ²	R ³	<i>t</i> (h)	yield (%) ^b
1 ^c	1a	H	H	H	6	82 (77)
2	1b	Me	–	–	2.5	89
3	1c	F	–	–	2.5	87
4	1d	–	Et	–	2	86
5	1e	–	–(CH ₂) ₅ –	–	2.5	84
6 ^d	1a	H	H	H	2	84

^aReaction conditions: substrate (0.6 mmol), H₂O (6 mmol), [HDBU][BenIm] (0.6 mmol), and CO₂ (1 bar, balloon) at 80 °C.

^bDetermined by GC using an internal standard; the yield in parenthesis is an isolated yield. ^cReaction conditions: **1a** (6 mmol, 1.1 g), H₂O (60 mmol), [HDBU][BenIm] (6 mmol), and CO₂ (1 bar, balloon) at 80 °C. ^d[HDBU][BenIm] was used for the fifth time.

this reaction proceeded on a 10 mmol scale of **1a**, and an 82% yield of **2a** was obtained after 6 h (entry 1). Diyne alcohols bearing either electron-donating (entry 2) or electron-withdrawing groups (entry 3) reacted smoothly with water under the optimized conditions, and the corresponding products **2b** and **2c** were obtained in 89% and 87% yield, respectively. When there was a large substituent group at R² or R³ (e.g., ethyl or cyclohexyl), the reaction also gave the desired product in high yield (entries 4 and 5). Moreover, [HDBU][BenIm] could be recycled easily without significant loss of catalytic activity after the fifth time (entry 6).

In conclusion, a strategy for the highly efficient synthesis of 3(2*H*)-furanones by hydration of diyne alcohols catalyzed by base-functionalized ionic liquids under atmospheric-pressure CO₂ has been developed. Notably, the best range of basicities of catalysts was predicted prior to the experiment. Furthermore, the catalytic reactivity of protic ILs (e.g., [HDBU][BenIm]) was better than that of aprotic ILs (e.g., [N₄₄₄₄][BenIm]). Through a combination of NMR spectroscopic investigations and quantum-chemical calculations, we found the moderate basicity to be the main reason for such high catalytic activity. Finally, this method could be extended to other diyne alcohols,

and [HDBU][BenIm] is reusable. The method developed in this work paves the way for other CCU processes and base-catalyzed reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08895.

Experimental procedures and DFT calculation details (PDF)

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Notes

The authors declare no competing financial interest.

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