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Catalysis by β-Cyclodextrin Hydrate – Synthesis of 2,2-Disubstituted 2*H*-Chromenes in Aqueous Medium

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Abstract: A cost-effective, operationally simple and eco-compatible protocol for the one-pot synthesis of photochromic pyrans by the reaction of propargyl alcohols as well as propargyl ethers with differently substituted phenols under ambient atmosphere in aqueous medium has been developed using β-cyclodextrin hydrate as an efficient, recyclable and stable catalyst. This is the first report where β-cyclodextrin hydrate acted as a catalyst for an organic transformation but β-cyclodextrin alone failed.

Keywords: aqueous-phase catalysis; cyclodextrins; green chemistry; organic catalysis; regioselectivity; synthetic methods

Introduction

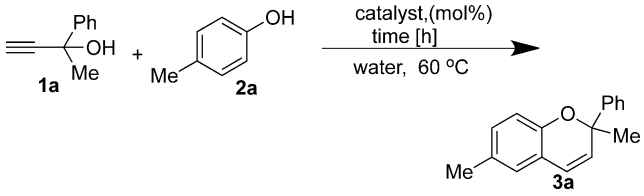
The development of novel methods and catalysts for important organic reactions always remains a formidable challenge to organic chemists due to the widespread applicability of the reaction products in the pharmaceutical industry and academia. The art of performing efficient chemical transformations by identifying alternative reaction conditions utilizing less toxic and inexpensive metal-free catalysts and avoiding the use of organic solvents as reaction medium represents a fundamental target of modern organic synthesis. Presently organic reactions in the aqueous phase[1] have attracted the attention of researchers due to specific advantages of water as an environmentally benign and economically affordable solvent. However, the fundamental problem to perform organic reactions in aqueous medium is the poor miscibility of many organic substrates with water. Cyclic oligosaccharides possessing hydrophobic cavities are well known as supramolecular catalysts, which by reversible formation of host-guest complexes, activate the organic molecules and thus efficiently catalyze the reactions under milder conditions as compared to their homogeneous counterparts, often with improved selectivity. Cyclodextrins (CDs) and crown ethers are examples of those biomimetic catalysts used extensively in many novel transformations with high yield and good selectivity. There are several reports[2] where CDs are used for the synthesis of important classes of biologically active heterocycles like thiazoles, quinoxalines, quinazolins, oxindoles, tryptanthrin and azepins. But surprisingly β-cyclodextin hydrate, which is much cheaper than cyclodextrins, has not yet been used as a catalyst to date to the best of our knowledge.

2*H*-Chromenes (2*H*-benzopyran derivatives) constitute an important class of compounds as they are present as a structural backbone in many natural products,[3–5] biologically active pharmaceutical and medicinal compounds such as anti-HIV,[6a] antitumor,[6b] antibacterial/antimicrobial,[6c,d] fungicidal,[6e] and insecticidal agents,[6f] health-promoting phytochemicals such as antioxidants,[6g] and polyphenols.[6h] In addition, they have also been extensively used as photochromic materials in diverse fields including laser dyes, organic light emitting devices (OLEDs), optical brighteners, organic scintillators, triplet sensitizers and fluorescence probes.[7] Owing to the diverse range of interesting properties and important applications, the development of synthetic strategies for the construction of the 2*H*-benzopyran skeleton has received significant attention at all times. Along with the classical methods,[4] many new methods have been developed[8,9] in recent times where tremendous emphasis is put on metal-catalyzed annulations such as hydroarylation.[9] But there is still a demand for new metal-free, economically viable and eco-compatible protocols applicable to a wide range of substrates. We report herein for the first time an aqueous phase synthesis of 2*H*-chromenes under metal-free conditions using β-cyclodextrin hydrate (to be cited as β-CD hy-

drate hereafter) as a reusable biomimetic catalyst with a broad substrate scope. This is going to be the first report of using β-cyclodextrin hydrate as a catalyst for an organic transformation which is much superior to β-cyclodextrin.

Results and Discussion

When an equimolecular mixture of 2-phenylbut-3-yn-2-ol (**1a**) and *p*-cresol (**2a**) was heated in water at 60 °C in the presence of β-CD hydrate, 2,6-dimethyl-2-phenyl-2*H*-chromene (**3a**) was obtained (Scheme 1).



Scheme 1. Reaction of 2-phenylbut-3-yn-2-ol (**1a**) with *p*-cresol (**2a**) using different catalysts.

This reaction was optimized using some analogous catalysts in varying amounts and different time intervals. The results are summarized in Table 1.

Table 1. Optimization of β-CD hydrate catalyzed heterodomino reaction between 2-phenylbut-3-yn-2-ol (**1a**) and *p*-cresol (**2a**).

Entry	Catalyst	Mol%	Time [h]	Yield of **3a** [%]
1	β-CD	10	10	–
2	γ-CD	10	10	trace
3	α-CD	10	10	30
4	β-CD hydrate	2	8	65
5	β-CD hydrate	4	6	85
6	β-CD hydrate	7	6	87
7	18-crown-6	4	10	56
8	18-crown-6	7	10	57

It is important to note that there was no reaction when an equimolecular mixture of **1a** and **2a** was heated at 60 °C in water in the presence of 10 mol% of β-CD (entry 1). The reaction was extremely sluggish in the presence of 10 mol% of γ-CD (entry 2). But the same reaction produced **3a** in 30% yield when it was done with 10 mol% of α-CD (entry 3). Surprisingly, the yield of the reaction was dramatically increased to 65% (entry 4) when β-CD hydrate was used as a catalyst in lesser amount (2 mol%). Further increase of the amount of β-CD hydrate to 4 mol% brought about the increment of yield to 85% (entry 5) in lesser time. With further increase of the catalyst amount to 7 mol%, the yield of the reaction remained more or less same (entry 6).The yield was not satisfactory when 18-crwon-6 was used as a catalyst (entries 7 and 8). The aforesaid reaction did not occur in absence of any catalyst. Thereby the importance of β-CD hydrate in terms of its catalytic activity was firmly established. Owing to the poor solubility of β-CD in water at 25 °C (1.84%, w/v),[10] the catalyst remained sparingly soluble at room temperature but became soluble at the reaction temperature (60 °C) in aqueous medium. Therefore, when the reaction was complete, the reaction mixture was cooled to room temperature to precipitate the catalyst and ethyl acetate (20 mL) was added to dissolve the product where the catalyst (β-CD hydrate) remained insoluble. So the catalyst was separated simply by filtration. It was washed thoroughly with EtOAc, dried at 100 °C for one hour and used for the next reaction. It was successfully recycled with little variation of yield (Figure 1). Due to its sparing solubility at room temperature and complete miscibility with the reaction medium at the elevated temperature, β-CD hydrate seems to behave as a homogeneous catalyst during the reaction but offers the advantage of a heterogeneous catalyst towards its separation and isolation from the reaction mixture. The reactions took place in aqueous condition and did neither require inert environment nor any organic co-solvent as the reaction medium. It needs an eco-friendly solvent, namely, ethyl acetate, for the isolation of the product. Moreover, the reactions are of high atom-economy and generate water as the sole and innocuous by-product. Therefore, the present protocol also bodes for eco-compatibility which bears immense relevance to the improvement of environmental performance. The

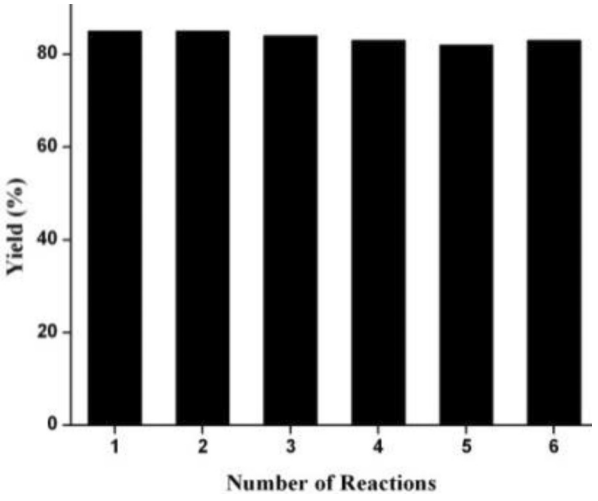
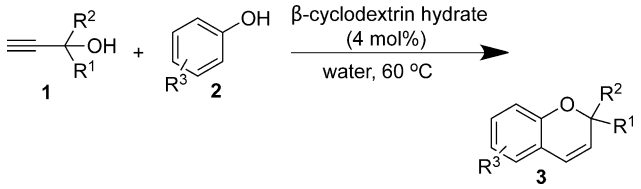
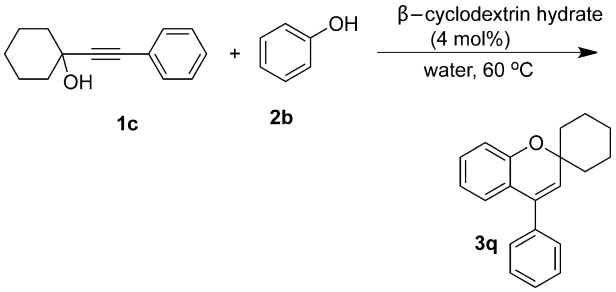


Figure 1. Recycling of β-CD hydrate using **1a** (2 mmol), **2a** (2 mmol) and β-CD hydrate (4 mol%) as catalyst at 60 °C for 6 h in water; the yield is of the isolated product **3a**.



Scheme 2. Synthesis of 2,2-disubstituted 2*H*-chromenes (**3**) through one-pot reaction between **1** and **2** in aqueous medium using β-CD hydrate as catalyst.



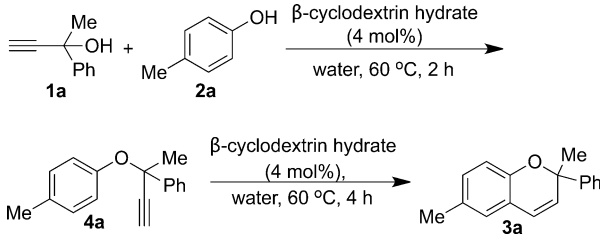
Scheme 3. Construction of the 2,2-spirocyclic 2*H*-chromene framework.

eco-compatibility of this protocol has been assessed in terms of *E*-factor, mass intensity, atom economy and atom efficiency (see the Supporting Information).

The remarkable recyclability and superior catalytic activity of β-CD hydrate prompted us to extend the applicability of this newly developed protocol. Therefore, we carried out systematic investigations on the synthesis of 2*H*-chromenes **3** through the reactions of various propargyl alcohols **1** with differently substituted phenols **2** using β-cyclodextrin hydrate (4 mol%) as a catalyst under the optimized reaction conditions (Scheme 2). The results are shown in Table 2.

As shown in Table 2, a wide variety of the substrates underwent regioselective heterodomino reaction in the presence of β-CD hydrate in aqueous medium to afford the 2*H*-chromenes **3** in good yield. *p*-Cresol (**2a**) reacted with substituted α-alkynols **1a** and **1b** to produce the corresponding *gem*-disubstituted 2*H*-chromenes in good yield (entries 1 and 2). Unsubstututed phenol **2b** (entries 3 and 4) and the sterically congested phenol **2c** bearing an alkyl substituent at the *o*-position (entries 5 and 6) also reacted smoothly in this protocol. Interestingly, the bromo substituent in **2d** remained totally unaffected under the present conditions (entries 7 and 8) and afforded **3g** and **3h**, respectively, with satisfactory yield. *p*-Chlorophenol **2e** was found to be problematic[6h] in some reports, but it responded efficiently in the present method and afforded the corresponding pyrans **3i** and **3j** with good yield (entries 9 and 10). *p*-Methoxyphenol **2f** also produced the methoxypyrans **3k** and **3l** with high yield (entries 11 and 12) where the methoxy group remained unaffected and the course of the reaction was totally guided by the *o*-directing effect of the phenolic-OH moiety. The present method was extended to naphthols **2g** and **2h**, where the corresponding photochromic naphthopyrans (**3m**–**3o**) were produced in quite good yield (entries 13–15). The uniqueness of the present method is also associated with the efficient preparation of bis-benzopyran derivative **3p** from quinol **2i** (entry 16). This protocol was successfully utilized for the construction of a novel and unprecedented 2,2-spirocyclic 2*H*-chromene skeleton (Scheme 3) from an appropriate propargyl alcohol **1c**.

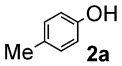
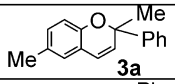
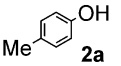
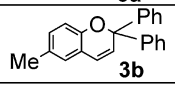
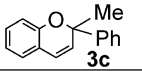
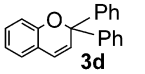
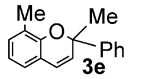
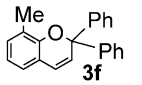
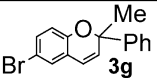
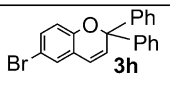
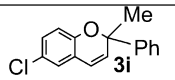
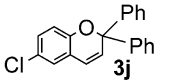
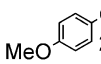
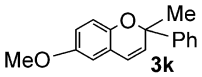
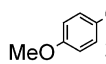
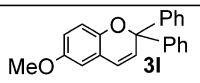
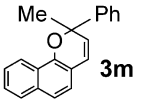
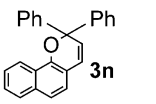
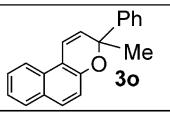
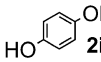
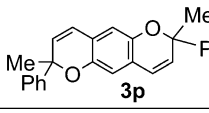
In course of the aforesaid investigation, it was found that C−C bond formation took place exclusively at the *o*-position with respect to the phenolic-OH group in spite of the availability of the more accessible *p*-positions in the substrates **2b** and **2c**. So we speculated that the aryl propargyl ether was initially formed in the first step followed by ring closure in a 6-*endo*-*dig* fashion through C−C bond formation *via* the intramolecular nucleophilic attack at the C≡C bond by the electron-rich proximal *o*-carbon of the aromatic ring. Indeed, when the reaction was run for a limited duration, we were able to isolate the aryl propargyl ether **4a** as the plausible intermediate. When **4a** was further subjected to the optimized reaction condition, **3a** was obtained as the product. Thus the intermediacy of **4a** in the said reaction was clearly established (Scheme 4).



Scheme 4. Intermediacy of aryl propargyl ether.

It is extremely important to note that although commercially available β-CD hydrate (Aldrich) came out as an efficient catalyst for the aforesaid reaction in aqueous medium, β-CD failed miserably (entry 1 *versus* entries 4–6 in Table 1). According to an early report,[11a] β-CD hydrate contains exchangeable hydrogen atoms associated with a proton conductivity similar to that of hydrated proteins. Some water molecules are present inside the hydrophobic cavity of β-CD hydrate along with some outside forming an extended hydrogen bonding network. This provides an efficient path for the long range movement of protons which is responsible for the protonic conductivity *via* a concerted and co-operative translocation of protons through the so-called flip-flop hydrogen bond.[11b] The acidity of the residual water molecules inside the hy-

Table 2. Reaction of different phenols with propargyl alcohols under the optimized reaction conditions using β-CD hydrate as catalyst.

Entry	R^1	R^2	Propargyl alcohol (**1**)	Phenol (**2**)	Product (**3**)	Time [h] / Yield [%][a]
1	Ph	Me	**1a**	 **2a**	 **3a**	6 / 85
2	Ph	Ph	**1b**	 **2a**	 **3b**	5 / 86
3	Ph	Me	**1a**	 **2b**	 **3c**	6 / 80
4	Ph	Ph	**1b**	 **2b**	 **3d**	5 / 78
5	Ph	Me	**1a**	 **2c**	 **3e**	6 / 78
6	Ph	Ph	**1b**	 **2c**	 **3f**	6 / 80
7	Ph	Me	**1a**	 **2d**	 **3g**	7 / 76
8	Ph	Ph	**1b**	 **2d**	 **3h**	7 / 78
9	Ph	Me	**1a**	 **2e**	 **3i**	7 / 76
10	Ph	Ph	**1b**	 **2e**	 **3j**	7 / 77
11	Ph	Me	**1a**	 **2f**	 **3k**	6 / 81
12	Ph	Ph	**1b**	 **2f**	 **3l**	5 / 82
13	Ph	Me	**1a**	 **2g**	 **3m**	5 / 80
14	Ph	Ph	**1b**	 **2g**	 **3n**	5 / 77
15	Ph	Me	**1a**	 **2h**	 **3o**	6 / 82
16	Ph	Me	**1a**	 **2i**	 **3p**	7 / 75

[a] Yield of the isolated pure products, fully characterized spectroscopically.

Table 3. Acidity measurements.

Substance	pH at 30 °C	pH at 60 °C
β-CD	6.12	5.98
β-CD hydrate	6.36	5.34

drophobic cavity of β-CD hydrate is consequently enhanced. The reactions did neither occur in the absence of β-CD hydrate nor under the non-aqueous solid phase condition with catalytic as well as stoichiometric amounts of β-CD hydrate. Moreover, not a trace of **3a** was obtained when **4a** was heated alone in water at 60 °C in the absence of β-CD hydrate. Therefore, the essentiality of β-CD hydrate in aqueous medium for promoting both the steps was firmly substantiated. It was indeed a matter of surprise to note that the reactions took place smoothly in the presence of β-CD hydrate but not in the presence of β-CD. In search for the answer of this puzzle we first measured the pH of the aqueous media at room temperature (30 °C) and at the reaction temperature (60 °C) containing β-CD and β-CD hydrate separately in the same concentration of the reaction mixture (Table 3). The pH of the solution containing β-CD hydrate at the reaction temperature was found to be lower indicating higher acidity of the reaction medium. From this observation it appeared that the acidity of the medium might be crucial. But the reactions between **1a** and **2a** totally failed in media of these pH values in the absence of β-CD hydrate. Therefore, apart from imparting acidity, a more crucial role of β-CD hydrate was anticipated.

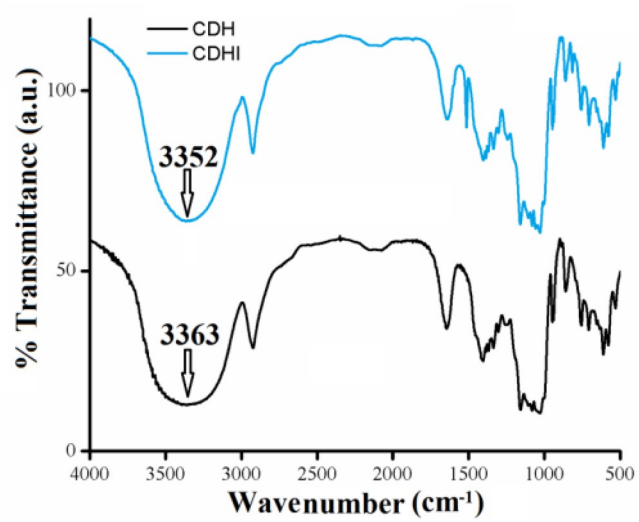
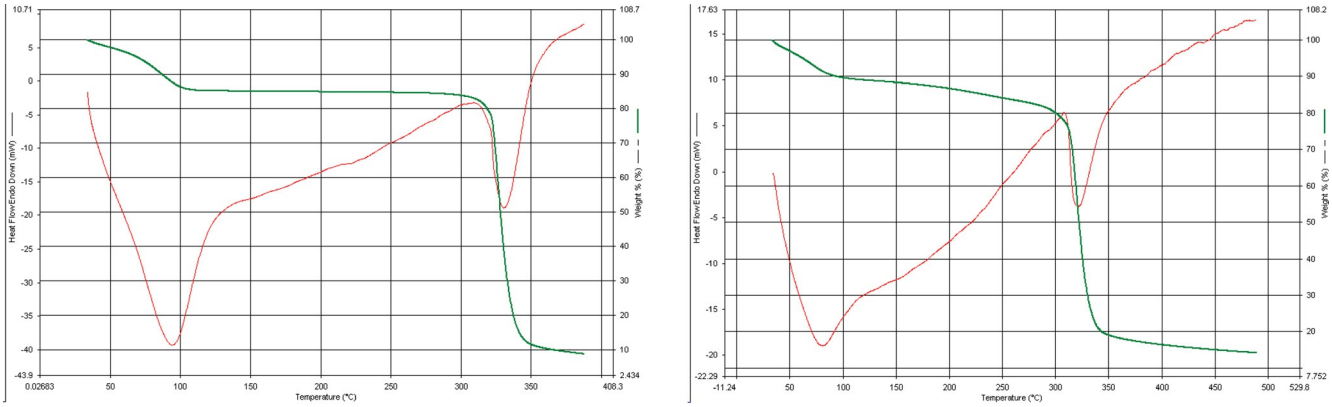


Figure 2. Comparison between FT-IR spectra of β-CD hydrate (CDH) and inclusion complex of **1a** with β-CD hydrate (CDHI).

Then we speculated that *p*-cresol (**1a**) might form an inclusion complex with β-CD hydrate. The FT-IR spectra of β-CD hydrate and the inclusion complex of **1a** in β-CD hydrate (Figure 2) looked similar, analogous to the observations made by Li et al.[12] A broad band centered at 3363 cm^{-1} appeared due to $\nu_{str}O{-}H$ of β-CD hydrate, which was found to be narrowed in the FT-IR spectrum of the inclusion complex and appeared at a lower frequency (3352 cm^{-1}). These observations provided a good indication of the formation of the inclusion complex, which was a common phenomenon observed by many researchers during the syntheses of the inclusion complexes of different guest molecules with β-cyclodextrin as host.[12–15]

The TGA curve (Figure 3a) of β-CD hydrate showed a sharp weight loss of about 15% around 110 °C due to the loss of water molecules, but no further weight loss was observed up to 300 °C. But in the case of the 1:1 inclusion complex of **1a** with β-CD hydrate (Figure 3b), because of the hydrogen bonding interaction between phenol molecules and water molecules present in the cavity of β-CD hydrate, the TGA curve depicted a sharp weight loss of about



3a 3b

Figure 3. a) TGA curve of β-CD hydrate and b) 1:1 inclusion complex of **1a** with β-CD hydrate.

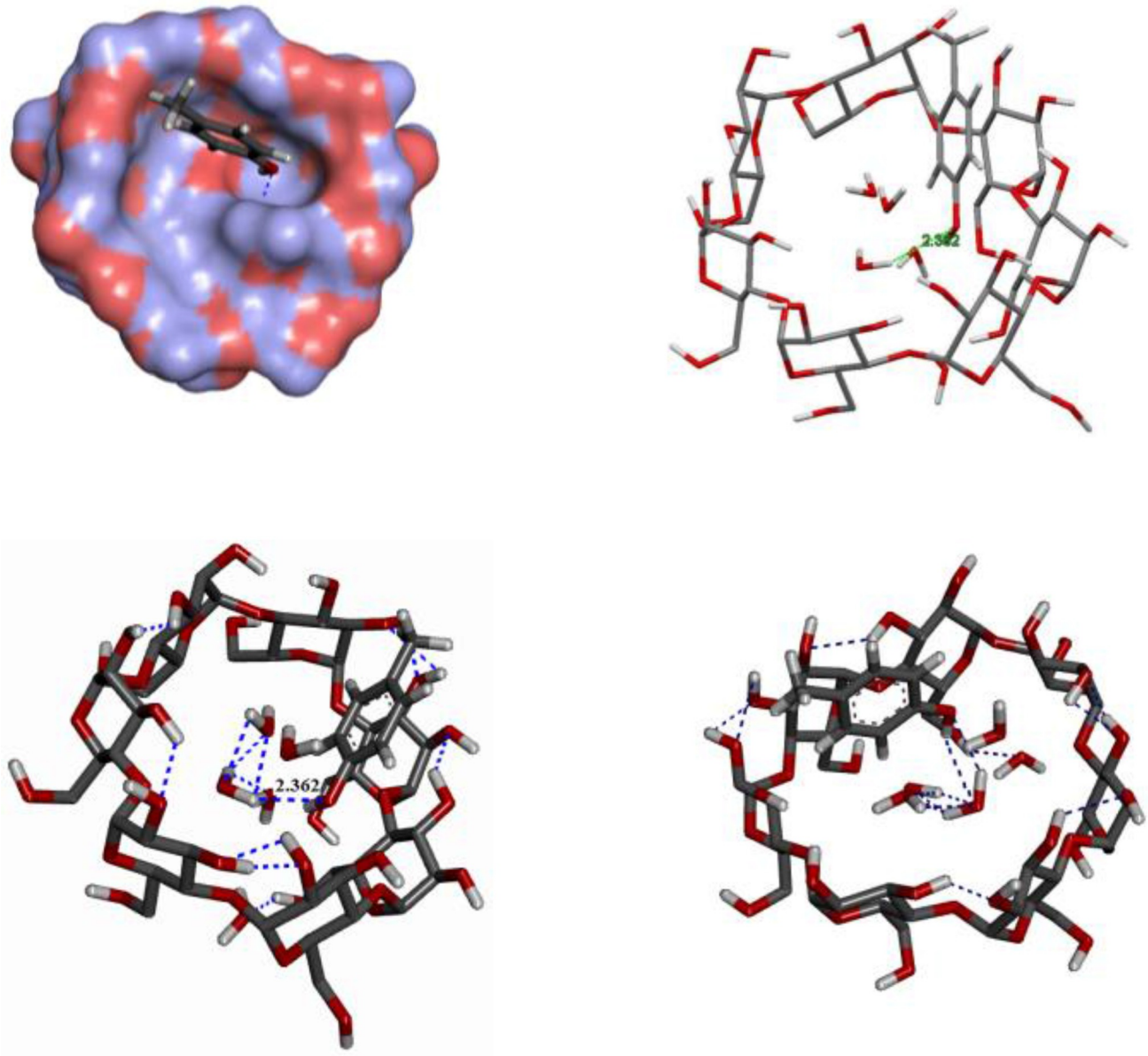


Figure 4. The most stable complex of *p*-cresol **1a** docked into the cavity of β-CD hydrate in different modes.

10% due to the loss of non-hydrogen bonded water molecules. Thereafter a slow weight loss was observed due to the loss of hydrogen bonded molecules. Also the TGA curve of β-CD[16] was distinctly different from that of the β-CD hydrate as there was no question of any initial water loss in the case of β-CD. It is extremely important to note that when β-CD hydrate, pre-heated at 130 °C for 4 h (where the initial loss of water was supposed to be complete), was used in the present aqueous reaction medium in place of commercially available β-CD hydrate, the reaction between **1a** and **2a** did not occur at all. Therefore, the presence of water molecules inside the cavity of β-CD hydrate was proved to be essential for the proposed reaction.

Due to the presence of water molecules within the cavity of β- CD hydrate, it was speculated that the hydrogen bonding interaction between the water and guest molecules might facilitate the inclusion of the guest within the host cavity. From the molecular docking experiments (PDB ID: ARUXOA), it was observed that **1a** and **2a** had a different affinity to β-CD hydrate with a preferred orientation of the ligands inside its cavity: **1a** was more included than **2a** within the cavity. Also **1a** formed one hydrogen bond (2.362 Å) with the water molecules present within the cavity of β- CD hydrate (Figure 4) whereas **2a** formed two hydrogen bonds (2.418 and 2.328 Å) with the -CH_2OH group located near the wider side (secondary hydroxy rim) (Figure 5).

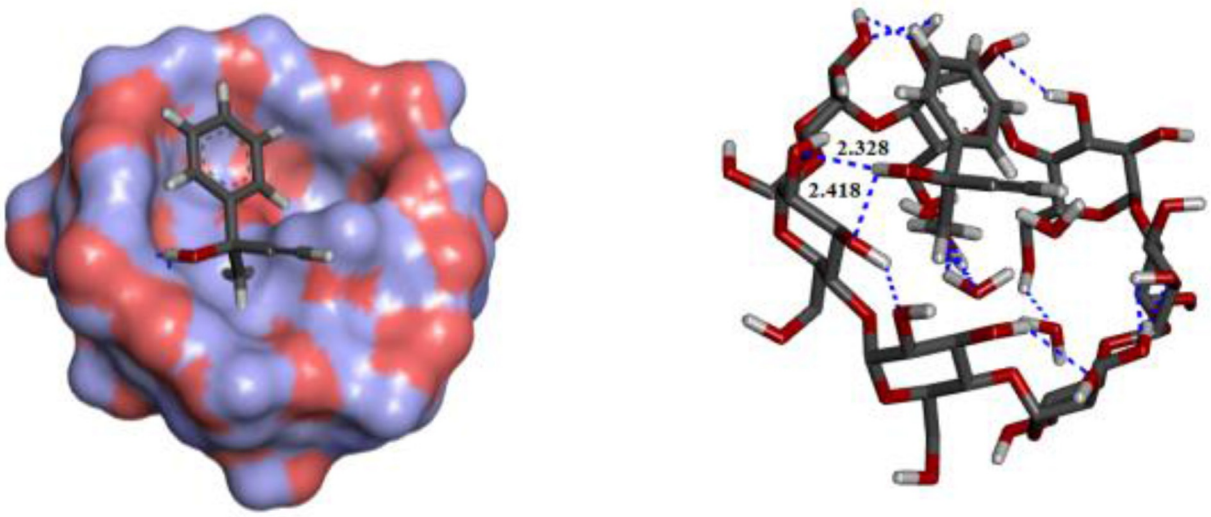
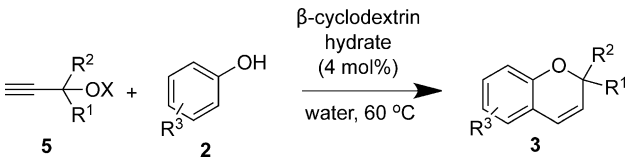


Figure 5. The most stable complex of propargyl alcohol **2a** docked into the secondary hydroxy rim of β-CD hydrate in different modes.

Hydrogen bonding of the phenolic-OH group of **1a** with the water molecules inside the cavity of β-CD hydrate as a consequence of inclusion might increase its nucleophilic property. As a consequence, nucleophilic attack by **1a** on **2a** is facilitated. ^{1}H NMR titration experiments were also performed using **1a** as guest and β-CD hydrate as host. We observed very small changes in the chemical shift values of the hydrogen atoms of both the guest and host molecules (see the Supporting Information). On the basis of the aforesaid experimental findings, the essential presence of β-CD hydrate for the aforesaid chemical transformation is quite evident. But the phenomenon of "inclusion" in this reaction is only a hypothesis because no direct and full evidence could be given. Although the exact reaction pathway and mode of catalysis still remain unclear to us, the synthetic importance of this β-CD hydrate-mediated protocol has been well-established and its widespread applicability is further substantiated with the following observations.

In a recent report[17] we noted that an ether group acted as a leaving group during Ni-catalyzed cross-coupling of aryl and benzyl methyl ethers with organoboron reagents. Therefore, we intended to extend this protocol to propargyl ethers **5** as substrates (Scheme 5). The results are presented in Table 4.



Scheme 5. Synthesis of 2,2-disubstituted 2*H*-chromenes from propargyl ethers.

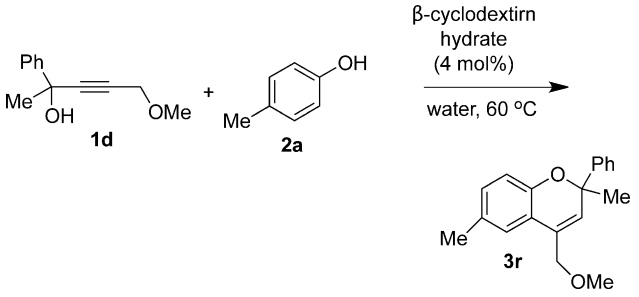
Table 4. Synthesis of 2,2-disubstituted 2*H*-chromenes from propargyl ethers.

Entry	R^1	R^2	X	R^3	Product	Time [h]/ Yield [%][a]
1	Ph	Me	Me	4-Me	**3a**	10/78
2	Ph	Me	Et	H	**3c**	10/74
3	Ph	Ph	Et	2-Me	**3f**	9/72
4	Ph	Me	TBDMS	4-Br	**3g**	9/76
5	Ph	Ph	TBDMS	4-Cl	**3j**	10/67
6	Ph	Me	$CH(Me)_2$	4-OMe	**3k**	9/74
7	Ph	Me	$(CH_2)_4$-CH_3	2-Me	**3e**	9/76
8	Ph	Me	$(CH_2)_4$-CH_3	4-Cl	**3i**	11/69
9	Ph	Ph	CH_2-CH=CH_2	4-OMe	**3l**	10/72
10	Ph	Ph	CH_2-CH=CH_2	4-Br	**3h**	10/70

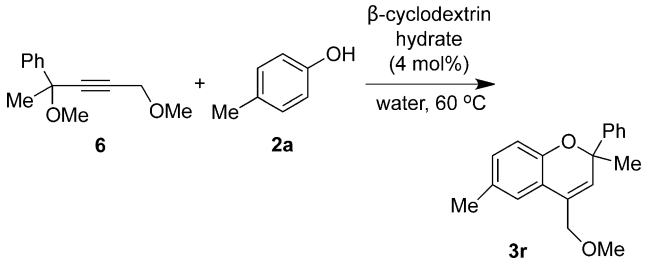
[a] Yield of the isolated pure products, fully characterized spectroscopically.

It was evident from Table 4 that the aforesaid reaction took place efficiently with differently substituted propargyl ethers although it took a longer time than with the respective alcohols. The reactions did not depend much on the electronic nature and steric bulk of the substituent X. With the substrate **1d** bearing both 3°-propargylic OH and 1°-propargylic OMe moieties, initial etherification took place exclusively by the displacement of the 3°-OH group leaving behind the 1°-OMe unaffected (Scheme 6) in the product **3r**. This study also proved that the same protocol was applicable to the propargyl alcohols with internally substituted acetylenic linkage also.

The propensity of the 3°-center towards this reaction was elegantly demonstrated in the reaction of the substrate **6** where the 3°-propargyl methyl ether participated regioselectively leaving behind the 1°-propargyl methyl ether intact (Scheme 7).



Scheme 6. Reactivity of 3°-OH group of propargyl alcohol.



Scheme 7. Regioselectivity of the reaction.

Conclusions

A cost-effective, operationally simple and eco-compatible protocol for the one-pot synthesis of photochromic pyrans by reaction of propargyl alcohols as well as propargyl ethers with differently substituted phenols under ambient atmosphere in aqueous medium has been developed using β-cyclodextrin hydrate as an efficient, recyclable and stable catalyst used for the first time to date. The method permits a convenient access to a wide range of structurally novel and functionally important 2,2-disubstituted-2*H*-chromene skeletons with great potential for future applications. Moreover, this is the first report of the application of β-cyclodextrin hydrate (in contrast to β-cyclodextrin) as an efficient catalyst for an organic transformation.

Experimental Section

General Procedure for Synthesis of 2,2-Disubstituted 2*H*-Chromenes

To a stirred suspension of the appropriate propargyl alcohol **1** or propargyl ether **5** (2.0 mmol) and phenol **2** (2.0 mmol) in 4 mL water, β-cyclodextrin hydrate (0.090 gm, 4 mol%) was added and the reaction mixture was stirred for the required period of time at 60 °C until the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to 5 °C, ethyl acetate (20 mL) was added to dissolve the product and the catalyst was separated simply by filtration for reuse. The residue (recovered catalyst) was thoroughly washed with EtOAc (4×5 mL) followed by water (2×10 mL). The aqueous reaction mixture was repeatedly extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with water (3×10 mL) and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure and was then further purified by filtration chromatography on a short column of silica gel using 1–2% ethyl acetate-hexane as eluent.

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