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Highly Chemoselective Baylis−Hillman and Aldol Reactions of 2*H*-Thiopyran-4(3*H*)-one Using Tertiary Amine Catalysts in Aqueous Media

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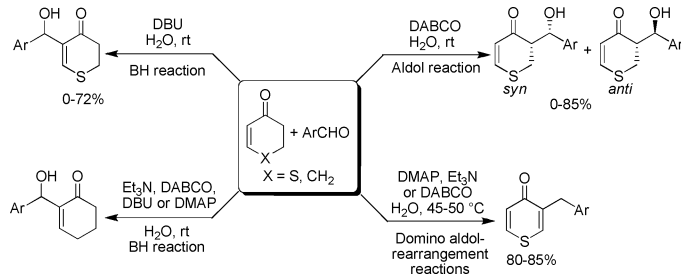
ABSTRACT



For the first time, the Baylis−Hillman (BH) reaction of 2*H*-thiopyran-4(3*H*)-one is investigated, and surprisingly, the reaction of 2*H*-thiopyran-4(3*H*)-one with aldehydes in the presence of different tertiary amines shows excellent chemo- and regioselectivity in water. At room temperature, DBU affords BH adducts, but with DABCO, aldol products were obtained. In the case of DABCO, Et_3N, or DMAP, domino aldol−rearrangement reactions occurred at 45−50 °C.

The organic reactions in aqueous media[1] have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheap, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents. Thus, development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[2]

The Baylis−Hillman (BH)[3] reaction is one of the most important reactions for C−C bond formation via reaction of activated alkenes with aldehydes in the presence of a catalytic amount of tertiary amines. Although the BH reaction furnishes densely functionalized products amenable to further structural elaboration from relatively simple starting materials,[4] it suffers from low reaction rates depending upon the reactivities of both the activated alkene and aldehyde and limited substrate scope. To overcome this problem, the reaction was carried out in a mixture of organic solvents with water as a cosolvent.[5]

In this paper, we have carried out the reaction of 2*H*-thiopyran-4(3*H*)-one **1** with aldehydes in the presence of tertiary amines as a catalyst in water. We have observed that reaction of **1** with aldehydes shows excellent chemo- and regioselectivity using different tertiary amines as a catalyst in water. Under the same reaction conditions, when cyclohex-2-enone **2** was used, only BH adducts **7** were obtained with any tertiary amines (Figure 1).

In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), BH adduct **3** was obtained as a sole product in short

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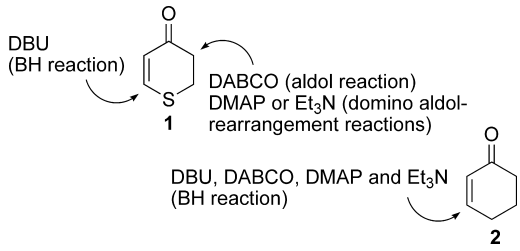
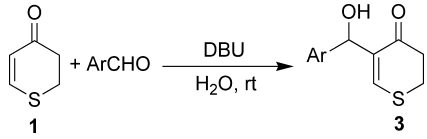


Figure 1. Chemo- and regioselectivity of **1** and **2** in reaction with aldehydes catalyzed with tertiary amines in water.

reaction time (Scheme 1). The scope of the DBU-catalyzed BH reaction was investigated by reacting **1** with a range of

Scheme 1. DBU-Catalyzed BH Reaction of **1**



benzaldehydes in water at room temperature (Table 1). In the case of strongly electron-withdrawing groups such as 4-nitrobenzaldehyde, the reaction was performed rapidly, and complex mixtures of products were produced. In the case of benzaldehydes with electron-releasing groups, the substrates were recovered without any changes after 5 days (Table 1, entry 6). Then temperature was raised to 45−50 °C, and unexpectedly complex mixtures of products were obtained. Also, the BH reaction of **1** with 4-fluorobenzaldehyde was investigated at 45−50 °C, and 3-(4-fluorobenzyl)-5-[(4-fluorophenyl)hydroxymethyl]-4*H*-thiopyran-4-one **4** was identified as an isolable product in low yield from a complex reaction mixture (Figure 2).

Table 1. DBU-Catalyzed BH Reaction of **1** at Room Temperature

entry	ArCHO	product	time (h)	yield (%)[a]
1	C_6H_5CHO	**3a**	8	68
2	4-ClC_6H_4CHO	**3b**	6	72
3	4-FC_6H_4CHO	**3c**	5	70
4	3-ClC_6H_4CHO	**3d**	7	67
5	3-BrC_6H_4CHO	**3e**	6	68
6	4-MeC_6H_4CHO	–	5 days	N.R.[b]
7	4-$NO_2C_6H_4CHO$[c]	–	2	–

[a] Yields refer to isolated products. [b] N.R. = No reaction. [c] A complex mixture of products was obtained.

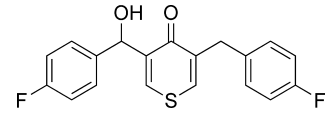


Figure 2. Structure of **4**.

Due to its easy availability, low cost, and high nucleophilicity, 1,4-diazabicyclo[2.2.2]octane (DABCO) is commonly used as a catalyst for the BH reaction.[3,6]

In continution, we were also encouraged to work on DABCO-catalyzed BH reaction of **1** with aldehydes in water at room temperature. Surprisingly, as shown in Scheme 2, in the case of electron-withdraweing substituted benzaldehydes, 3-[(4-aryl)hydroxymethyl]-2*H*-thiopyran-4(3*H*)-ones **5a**−**f** were obtained as the only product via aldol reaction in good to high yields with good to excellent *syn* selectivity in short reaction times (Table 2, entries 1−6). In the case of benzaldehydes with electron-releasing groups, there are no

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Scheme 2. DABCO-Catalyzed Aldol Reaction of **1**

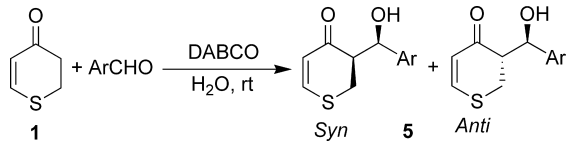


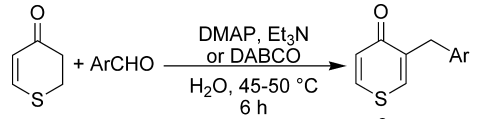
Table 2. DABCO-Catalyzed Aldol Reaction of **1**

entry	ArCHO	product	time (h)	yield (%)[a]	dr[b]
1	4-ClC_6H_4CHO	**5a**	4	85	>99/1
2	4-$NO_2C_6H_4CHO$	**5b**	5	80	>99/1
3	4-CNC_6H_4CHO	**5c**	5	77	60/40
4	2,4-$Cl_2C_6H_3CHO$	**5d**	3	83	>99/1
5	3-ClC_6H_4CHO	**5e**	8	75	95/5
6	3-$NO_2C_6H_4CHO$	**5f**	6	73	66/34
7	C_6H_5CHO	–	24	N.R.[c]	–
8	4-MeC_6H_4CHO	–	24	N.R.[c]	–
9	4-$MeOC_6H_4CHO$	–	24	N.R.[c]	–
10	*n*-PrCHO	–	24	N.R.[c]	–

[a] Yields refer to isolated products. [b] dr (*% syn/anti*) was determined by ^{1}H NMR spectroscopy analyses of the crude products. [c] N.R. = No reaction.

changes in substrates after 24 h (Table 2, entries 7−9). Then temperature was raised, and interestingly 3-(arylmethyl)-4*H*-thiopyran-4-one derivatives[7] **6** were obtained via domino aldol−rearrangement reactions (Scheme 3). Also, the reaction

Scheme 3. Et_3N, DMAP, or DABCO-Catalyzed Domino Aldol−Rearrangement Reactions of **1** at 45−50 °C



6a: Ar = C_6H_5, 85%
6b: Ar = 4-ClC_6H_4, 81%
6c: Ar = 2,6-$Cl_2C_6H_3$, 83%
6d: Ar = 4-MeC_6H_4, 81%
6e: Ar = 4-$MeOC_6H_4$, 80%

of butyraldehyde, an aliphatic aldehyde, with **1** was investigated at the same conditions, and the starting materials were recovered after 24 h (Table 2, entry 10).

The X-ray single-crystal structure analysis of 3-[(2,4-dichlorophenyl)hydroxymethyl]-2*H*-thiopyran-4(3*H*)-one **5d** (Figure 3) revealed that the major isomer possesses *syn* stereochemistry. The relative configuration of the racemic title compound is *R*,*R*.

In continution, other tertiary amine catalysts such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and Et_3N were used. At room temperature, there are no changes in the starting materials after 24 h. Then, temperature was raised

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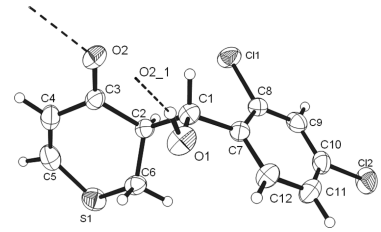
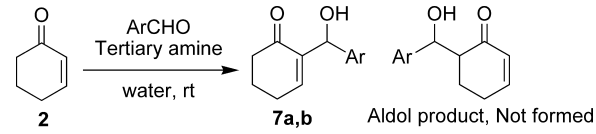


Figure 3. ORTEP representation of the crystal structure of **5d**.

to 45−50 °C, and compounds **6** were obtained in high yields as sole products, as shown in Scheme 3. Not only electron-withdrawing substituted benzaldehydes but also electron-releasing substituted benzaldehydes worked well.

The results persuaded us to investigate chemo- and regioselectivity in the reaction of cyclohex-2-enone **2**, as a similar structure of **1**, with aldehydes catalyzed with tertiary amines at the same conditions. As shown in Scheme 4, only

Scheme 4. Tertiary Amine-Catalyzed BH Reaction of **2** in Water



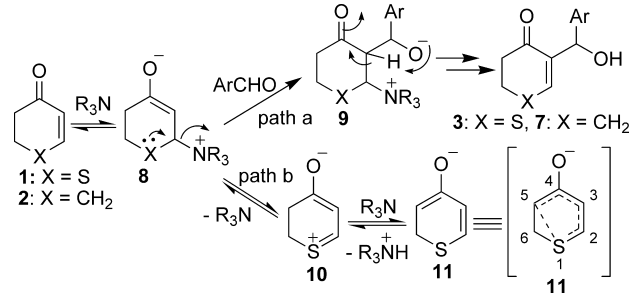
The yields of BH addacts (%)

ArCHO	DBU	DABCO	Et_3N	DMAP
a: C_6H_5CHO	52	50	78	46
b: 4-ClC_6H_4CHO	57	60	83	51

BH adducts **7** were obtained in the case of **2** using DBU, DABCO, Et_3N, or DMAP as the catalyst. The results revealed that DBU and DABCO show similar activity. Et_3N shows good efficiency in the BH reaction of **2** in water at room temperature.

In the most generally accepted mechanism[4,5a] of the amine-catalyzed BH reaction (Scheme 5, Path a), the rate-determin-

Scheme 5. Effect of the Stability of **8** and Neighboring S Atom on the Chemo- and Regioselectivity of Reaction



ing step is either the intramolecular proton transfer in the zwitterionic intermediate **9**[8] or the reaction of zwitterion **8** with aldehydes.[9] The rate of the generation of **8** is related to the nucleophilicity of amine, activity of alkene, and stability of zwitterion **8**. The results of Scheme 4 indicate that in the case of activated alkene **2** (X = CH_2) nucleophilicity of amine (DABCO, Scheme 4) works as well as the stability of **8** (DBU, Scheme 4). DBU is considered to be a non-nucleophilic hindered base, but because of the stability of zwitterion **12** through conjugation,[9] DBU worked well in the BH reaction (Figure 4). The results of Tables 1 and 2

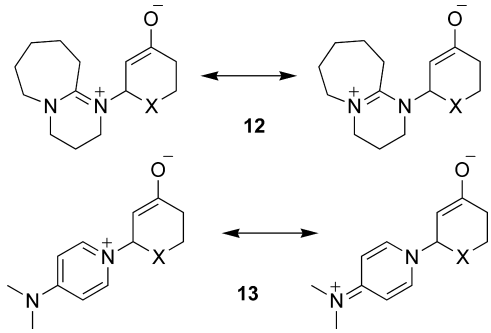
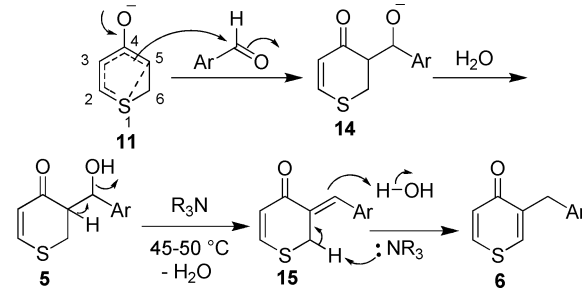


Figure 4. Stability of **12** and **13** through conjugation.

revealed that in the case of less activated alkene **1** (X = S) the stability of zwitterion **8** is the prominent factor in the chemo- and regioselectivity of the reaction.

As shown in Scheme 5 (path b), when X = S, an amine was removed from **8** by the neighboring sulfur atom participation. The lower the stability of the zwitterion **8**, the higher the rate of amine removal. Because of the stability of **12** (X = S) through conjugation, DBU acts as an efficient catalyst in the BH reaction of **1**. In the case of DMAP, although there is conjugation stability (Figure 4, **13**), the zwitterion **13** (X = S) is not more stable, and amine was removed because of loss of the aromaticity of pyridine. So, BH adducts were not produced in the DMAP-catalyzed reaction of **1** with aldehydes in water. Although DABCO is one of the most nucleophilic amines, the BH reaction did not occur in the DABCO-catalyzed reaction of **1** because of the lower stability of the zwitterion **8**, and interestingly, aldol products were produced. This can be attributed to, as shown in Scheme 6, a considerable cyclic conjugation in the enolate

Scheme 6. Plausible Mechanism for Aldol and Domino Aldol−Rearrangement Reactions of **1**



form **11**.[10] When the zwitterion **8** is not more stable, the species **11** control the reaction progress, and aldol reaction occurred.

As the same structure with thiophene, compound **11** with cyclic conjugation having a hydroxyl group on C-4 undergoes the reaction with aldehydes at C-5. The plausible mechanism is shown in Scheme 6. When temperature was raised, a water molecule was removed, and then by rearrangement of the double bond, compounds **6** were produced.

In conclusion, for the first time, the BH reaction of 2*H*-thiopyran-4(3*H*)-one **1**, a less-activated alkene, was investigated. Surprisingly the reaction of **1** with aldehydes in the presence of different tertiary amines shows excellent chemo- and regioselectivity in water. Also, this study revealed that the stability of β-ammonium enolate intermediate **8** plays an important role in the chemo- and regioselectivity of the reaction of less-activated alkene **1**. According to the stability of **12** through conjugation, DBU acts as an efficient catalyst in the BH reaction of **1**. However, because of the lower stability of **8**, DABCO, DMAP, and Et_3N act as a base, and an aldol reaction was performed. In the case of activated alkenes such as **2**, the nucleophilicity of amine works as well as the stability of **8** (X = CH_2), and only a BH reaction occurred.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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