

Switching the Reactivity of Dihydrothiopyran-4-one with Aldehydes by Aqueous Organocatalysis: Baylis–Hillman, Aldol, or Aldol Condensation Reactions[†]

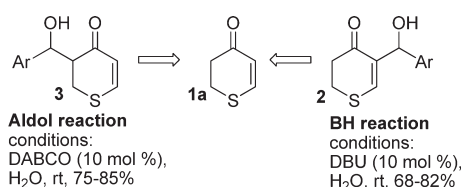
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ABSTRACT



An aqueous medium containing catalytic amounts of a tertiary amine was employed to direct the chemoselectivity of the reaction of aldehydes with 1a. With DBU, 2 was formed at room temperature as a rare exemplar of Baylis–Hillman reactions in heterocyclic enones. DABCO alternated the pathway toward an aldol reaction to form *syn/anti* mixtures of 3 with the *syn* isomers being the major products. With Et₃N, aldol condensation dominated.

Since its discovery in the early 1970s, the Baylis–Hillman (BH) reaction¹ has received significant attention from organic chemists due to the ability to produce densely functionalized molecules from relatively simple starting materials via an atom-economic one-pot procedure.² The

BH adducts have found many applications in the synthesis of natural products,³ bioactive molecules,⁴ and various heterocyclic⁵ and carbocyclic compounds.⁶ Extensive efforts have been devoted in recent years to overcoming the

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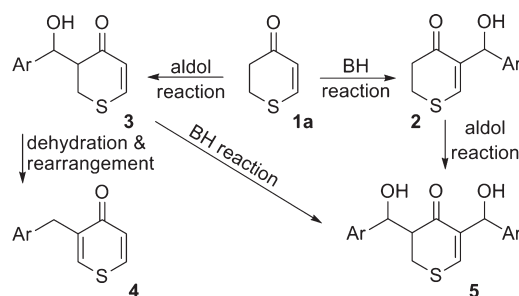
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inherent low reactivity of enones in BH reactions by the use of high pressure systems,⁷ microwave irradiation,⁸ ultrasonic waves,⁹ nonamine nucleophiles,¹⁰ solid-supported reagents,¹¹ ionic liquids,¹² Lewis acids,¹³ and organocatalysts.¹⁴ A particular improvement in BH reactions is gained by employment of aqueous media,¹⁵ the conditions known to boost the selectivity and reactivity of many synthetic organic transformations.¹⁶

Another limitation to BH reactions is the parallel competition of aldol reaction/condensation in the case of substrates with acidic α hydrogens.¹⁷ Moreover, utilization of heterocyclic enones with an electron-donating nature in BH reactions has still remained a challenge.² Because of our experience on thiopyran heterocyclic systems,¹⁸ we envisaged that enone **1a** would be an appropriate probe to tackle these limitations.¹⁹ As a result of our studies, we hereby disclose the potential of an aqueous organocatalytic system that can direct the reaction of **1a** with aldehydes to selectively undergo either BH or aldol reactions. To the best of our knowledge, this is the first report on BH and aldol reactions in the dihydrothiopyran-4-one system (Scheme 1).

Scheme 1. Competition of BH and Aldol Reactions in **1a**: Possibilities and Potentials



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A variety of conditions were examined to optimize the addition of **1a**²⁰ to benzaldehyde using different amines and solvents. The best results were obtained when DBU was added to an aqueous mixture of the reactants without organic solvents (Table 1). Under these conditions, catalytic quantities of DBU were effective to obtain **2a** within 8 h (entry 1). When other aldehydes bearing electron-withdrawing groups were used, products **2b–f** were obtained within the same time period (entries 2–6).

Table 1. BH Reactions of **1a** with Aldehydes

entry	Ar	product	time (h)	yield (%) ^a
1	C ₆ H ₅	2a	8	68
2	3-FC ₆ H ₄	2b	4	73
3	4-FC ₆ H ₄	2c	4	70
4	3-ClC ₆ H ₄	2d	7	67
5	4-ClC ₆ H ₄	2e	6	72
6	3-BrC ₆ H ₄	2f	6	68
7	2-thienyl	2g	4	62
8	2-NO ₂ C ₆ H ₄	2h	2	60
9	4-CF ₃ C ₆ H ₄	2i	1	52

^a Yields of isolated products.

Under the same conditions, aldehydes with a more electron-deficient nature disappeared faster. However, they gave lower yields of their respective BH adducts **2h–i** (entries 8–9), due to the effective competition of an aldol condensation reaction to give products of type **4**. This encouraged us to find the optimized conditions for the synthesis of **4** as well. Consequently, when we substituted DBU with DMAP (10%), high yields of various products **4** were obtained at room temperature within relatively short time periods (Table 2). In this case, electron-rich aldehydes such as 4-MeOC₆H₄CHO reacted sluggishly giving low yields of aldol products (entry 12).

With these results in hand, we were encouraged to investigate the feasibility of halting the aldol process before the dehydration step occurs. The experiments carried out with other amines in water showed that the use of DABCO

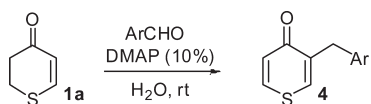
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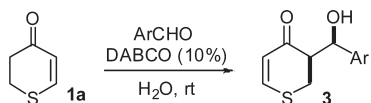
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(20) Compound **1a** was synthesized according to an available procedure. For details, see: Chen, C. H.; Reynolds, G. A.; Van Allen, J. A. *J. Org. Chem.* **1977**, 42, 2777.

Table 2. Aldol Condensations of **1a** with Aldehydes

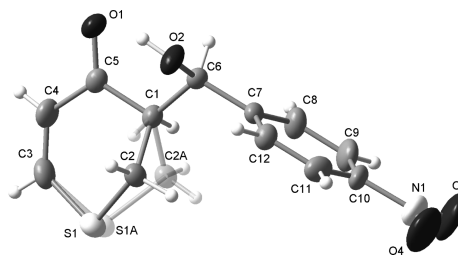
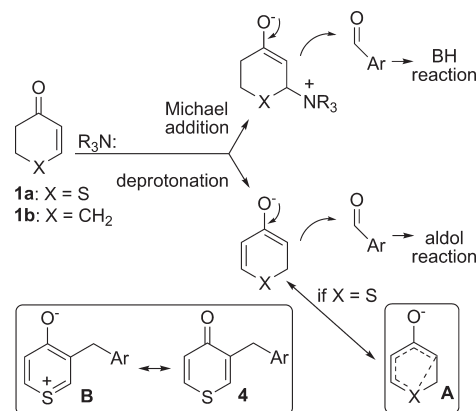
entry	Ar	product	time (h)	yield (%) ^a
1	2-thienyl	4g	9	87
2	2-NO ₂ C ₆ H ₄	4h	4	80
3	4-CF ₃ C ₆ H ₄	4i	4	85
4	3-NO ₂ C ₆ H ₄	4j	2	62
5	PhCH=CH	4k	8	92
6	2-furyl	4l	8	84
7	2-ClC ₆ H ₄	4m	8	75
8	2,3-Cl ₂ C ₆ H ₃	4n	8	85
9	2,4-Cl ₂ C ₆ H ₃	4o	5	89
10	2,6-Cl ₂ C ₆ H ₃	4p	8	82
11	3-NCC ₆ H ₄	4q	8	86
12	4-MeOC ₆ H ₄	4r	12	10

^a Yields of isolated products.**Table 3.** Aldol Reactions of **1a** with Aldehydes

entry	Ar	product	time (h)	yield (%) ^a (<i>syn/anti</i>) ^b
1	3-ClC ₆ H ₄	3d	8	75 (2:1)
2	4-ClC ₆ H ₄	3e	4	80 (2:1)
3	2-NO ₂ C ₆ H ₄	3h	4	85 ^c (4:1)
4	3-NO ₂ C ₆ H ₄	3j	4	83 (2:1)
5	2,4-Cl ₂ C ₆ H ₃	3o	3	85 (5:1)
6	4-NO ₂ C ₆ H ₄	3s	4	80 (3:1)
7	3-MeOC ₆ H ₄	3t	3	80 (2:1)
8	4-MeOC ₆ H ₄	—	12	—
9	4-MeOC ₆ H ₄	4r	10	35 ^d

^a Yields of isolated products. ^b Only the structure of the major *syn* stereoisomers is shown here. ^c 5% DABCO was used. ^d 50 °C.

directs the process toward selective removal of the proton of the α methylene group in **1a**. Hence, the addition of electron-deficient aldehydes to enone **1a** occurred to give good to high yields of *syn/anti* mixtures of **3** (Table 3). ¹H NMR analysis of the mixtures showed preferential formation of the *syn* stereoisomers over the *anti* counterparts in a ratio ranging from 5:1 to 2:1. It appears from the results that the stereoselectivity values correspond to the electron density of the starting aldehydes and grow as the electron deficiency increases. The *syn* stereochemistry for the major products was assigned based on their ¹H NMR spectra and verified by X-ray crystallography of product **3s** (Figure 1).

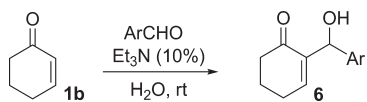
**Figure 1.** Structure of *syn* **3s** in the crystal. Displacement ellipsoids at the 50% probability level. Disorder in the thiopyran ring with alternative conformation (occupation 5.2(4)%) drawn transparent.**Figure 2.** Suggested mechanism: nucleophilicity versus basicity in enones with α acidic hydrogens.

In the case of **3t**, the minor *anti* isomer was also separated and characterized by spectroscopic methods. Under the same conditions, more electron-rich aldehydes remained intact (entry 8) or, at elevated temperatures, gave **4** (entry 9).

To rationalize these observations, two different pathways can be envisaged for the reaction of an amine with an enone like **1a**. The amine can either add to the conjugated C=C site as a Michael donor, a step which is accepted to occur initially in BH reactions,^{3,21} or remove the α hydrogen of the carbonyl group to trigger the aldol process (Figure 2). Therefore, it is not surprising if the more nucleophilic amines end up with the BH adducts, as we observed for DBU catalyzed reactions. At the other extreme, a bulkier amine such as DABCO could be expected to show more basicity and would prefer the aldol route.²²

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Table 4. BH Reactions of **1b** with Aldehydes

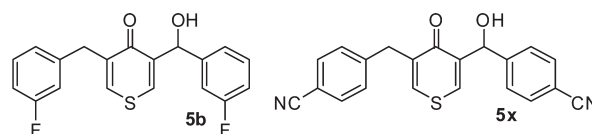
entry	R	product	time (h)	yield (%) ^a
1	C ₆ H ₅	6a	24	78
2	3-FC ₆ H ₄	6b	18	75
3	4-FC ₆ H ₄	6c	15	80
4	4-ClC ₆ H ₄	6e	15	82
5	3-BrC ₆ H ₄	6f	15	75
6	2-thienyl	6g	24	79
7	4-MeC ₆ H ₄	6u	24	68
8	Me(CH ₂) ₂	6v	15	80
9	Me ₂ CH	6w	18	82

^a Yields of isolated products.

If the proposed analogy is valid, one would expect that for enones with X = CH₂ (e.g., **1b**, Table 4) the aldol pathway becomes less important because the stabilizing homoaromaticity effect cannot exist for **1b** (in contrast to **1a** as shown with **A**; X = S)²³ and thus the enone is expected to be a relatively better Michael acceptor. Indeed, the spontaneous rearrangement of the C=C to the endocyclic position in the aldol condensation products could also be attributed to the aromaticity of **4** (as depicted for **B**).

To support this idea, BH reactions of cyclohexenone **1b** were evaluated under similar conditions. In the presence of DBU, DABCO, DMAP, or Et₃N the major observed process was the formation of the BH adducts **6**. In this case, Et₃N gave better results and therefore the reactions were carried out using this amine. This was the case not

(23) Homoaromaticity in the thiopyran system has been pointed out before: Vessally, E.; Kavian, H.; Arshadi, S.; Pirelahi, H. *J. Mol. Struct.* **2004**, 678, 171.

Scheme 2. Tandem BH-Aldol Synthesis of **5b** and **5x**

only for electron-deficient aryl aldehydes (entries 1–6) but also for electron-rich aromatic (entry 7) and aliphatic substrates (entries 8–9).

In conclusion, by using a nucleophilic amine in an aqueous environment, we accomplished a rare BH reaction in heterocyclic enone systems, which presumably due to a lower affinity for conjugate addition have been less prone so far to undergo BH reactions. To divert the process toward the alternative aldol pathway, we suppressed the conjugate addition (the BH route) by choosing a relatively bulkier amine which shows better basicity, which is required to initiate the aldol process. Currently, we are extending the methodology to the synthesis of products of type **5**, two of which are presented in Scheme 2. The application of the results in similar heterocyclic systems (**1**; X = NR, O) is under study and will be reported in due course.

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Supporting Information Available. Crystallographic data (excluding structure factors) for **3s** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No.841408. Copies of the data can be obtained free of charge via the Internet at <http://www.ccdc.cam.ac.uk/conts/retrieving.html>. Experimental procedures and spectral data of new compounds available free of charge via the Internet at <http://pubs.acs.org>.