Thiazolium Ylide-Catalyzed Intramolecular Aldehyde–Ketone Benzoin-Forming Reactions: Substrate Scope

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Received: March 23, 2004; Accepted: July 5, 2004

Dedicated to the memory of the late Professor Oyo Mitsunobu.

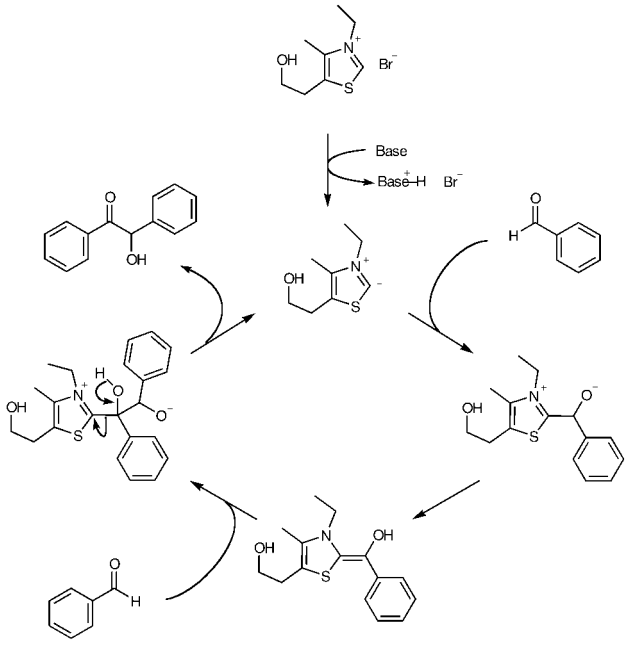
Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

Abstract: The scope and limitations of intramolecular benzoin-forming reactions of aldehydes and ketones catalyzed by the combination of a thiazolium salt and a base are described. After optimization of the reaction conditions, five- and six-membered cyclic acyloins were obtained in good to excellent yields and competing reactions such as intramolecular aldol reactions were suppressed. The analogous closure of seven-membered rings proved difficult.

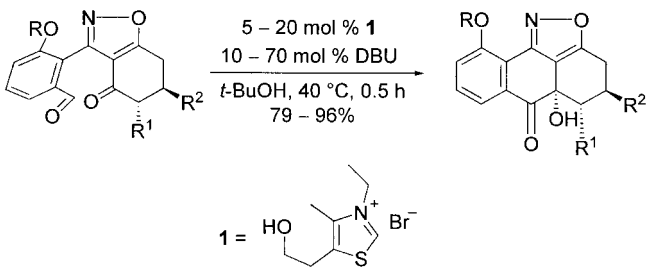
Keywords: benzoin; cyclization; ketones; organic catalysis; tertiary alcohols

It has long been known that thiazolium salts, in the presence of bases, catalyze benzoin-type reactions[1] of aldehydes *via* the mechanism proposed by Breslow in 1957 (Scheme 1).[2,3] Although the catalytically generated activated intermediate is broadly considered to be an acyl anion equivalent,[4] the electrophilic reaction partners have been essentially limited to aldehydes,[5] imines[6] or Michael acceptors, such as enones.[7]

Recently, we reported a cyclization *via* benzoin-type aldehyde–ketone coupling, affording tetracyclic products with an α-ketol function (Scheme 2).[8,9] This process, which proceeded with high efficiency under mild and convenient reaction conditions, enabled a novel and stereoselective approach to complex anthraquinone precursors. In addition to the utility of the products, we found it remarkable that, prior to our investigations, ketones had not been employed as electrophiles in benzoin-type couplings.[10] While we initially believed that our highly rigid systems were uniquely oriented for intramolecular reaction, thus allowing the use of ketones as electrophiles, we sought to explore these reaction conditions for further examples of intramolecular aldehyde–ketone benzoin-forming reactions.



Scheme 1. Proposed mechanism of thiazolium ylide-catalyzed reaction.



Scheme 2.

We now report that a wide variety of keto-aldehyde substrates cyclize in good yields under optimized reaction conditions. Remarkably, our preliminary results suggest that neither preorientation of the functional

 DOI: 10.1002/adsc.200404092

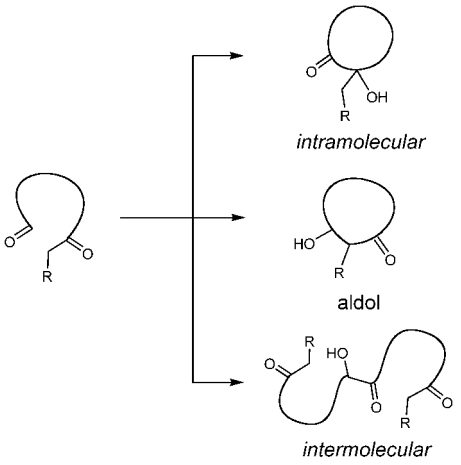
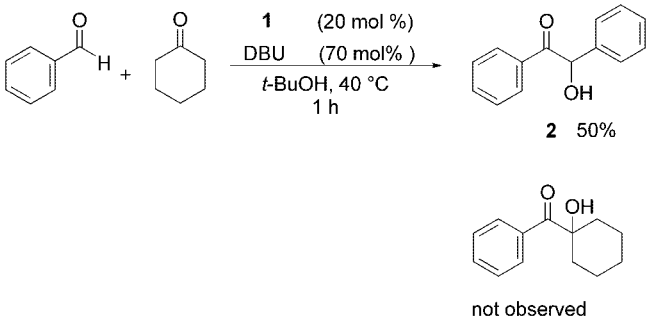


Figure 1. Competing reaction pathways.

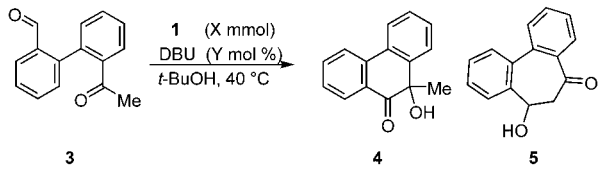


Scheme 3. *Intermolecular* benzoin-forming reaction.

groups nor absence of enolizable aldehydes are prerequisites for high reactivity. The expected by-products, dimeric benzoins and/or aldol products, are largely suppressed by improvements in the reaction conditions (Figure 1). Taken together, these results document a broad and highly useful scope for the intramolecular ketone–aldehyde benzoin-forming reactions under mild, convenient reaction conditions.

We first sought to examine whether ketones can generally serve as electrophiles in *intermolecular* benzoin-type reactions, a previously unreported process. Not unexpectedly, however, no isolable cross-coupled products were observed upon exposure of a mixture of benzaldehyde and cyclohexanone to benzoin catalysts and typical reaction conditions. Only benzoin **2** was obtained in 50% yield (Scheme 3).

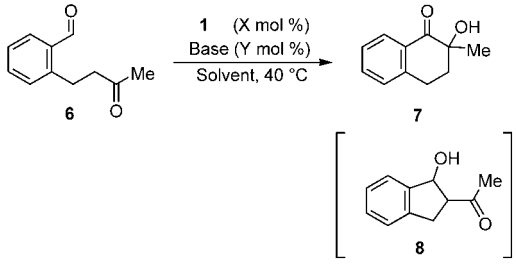
We therefore concentrated on the *intramolecular* reactions, and started with the reaction of the simple biaryl keto-aldehyde **3** (Scheme 4). Under our previously reported conditions,[9] the desired product **4** was obtained in low yield, accompanied by a significant amount of aldol product **5** (Table 1, Entry 1). After some experimentation, a simple means of suppressing the competing aldol reaction was found: the employment of DBU in substoichiometric quantities relative to the thiazolium salt (Entries 2 and 3). This presumably results in a decrease



Scheme 4.

Table 1. Reactions of biaryl substrate **3**.

Entry	X [mol %]	Y [mol %]	Time [h]	Yield [%]	
				4	**5**
1	20	70	1.5	65	26
2	20	40	1	81	9
3	25	20	1	90	5



Scheme 5.

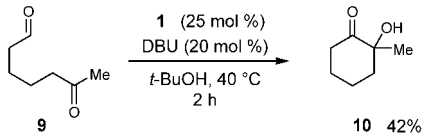
Table 2. Optimization of reaction conditions for keto-aldehyde **6**.

Entry	X	Base	Y	Solvent	Time [h]	Yield [%]
1	20	DBU	70	*t*-BuOH	1	63[a]
2	50	DBU	40	*t*-BuOH	0.5	81
3	50	Et_3N	40	*t*-BuOH	24	78
4	50	*t*-BuOK	40	*t*-BuOH	0.5	78
5	50	DBU	40	EtOH	1	66
6	50	DBU	40	DMF	0.5	68
7	50	DBU	40	THF	1	81
8	25	DBU	20	*t*-BuOH	2	89

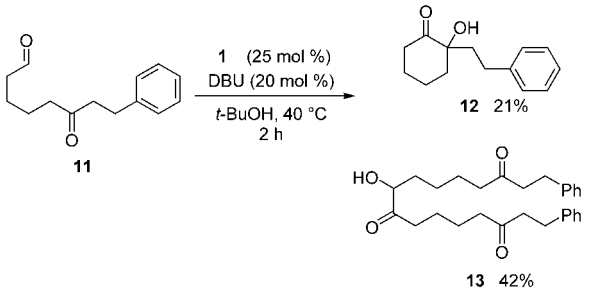
[a] The aldol product **8** was obtained in 8% yield.

in the overall basicity of the reaction medium, leading to a suppression of the undesired intramolecular aldol process.[11]

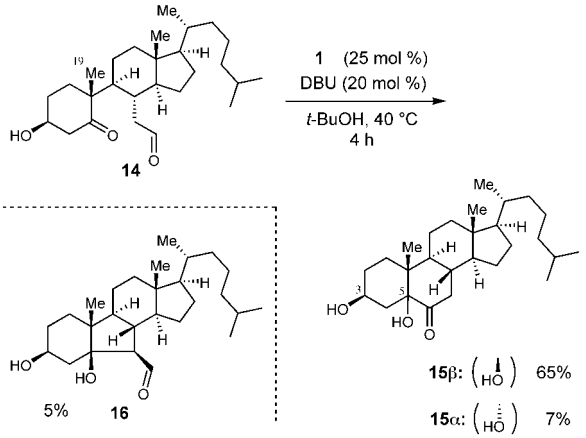
We were pleased to find that the reaction was not limited to ketones alpha to an aromatic ring, as exemplified by substrate **6** (Scheme 5, Table 2). Again, the relative amounts of thiazolium salt and base proved important (Entries 1 and 2). While the use of excess base gave the aldol side product, this competing process could be completely suppressed simply by reducing the relative amount of DBU, giving cyclized product **7** in 81% yield (Entry 2). The use of other bases was also possible: triethylamine and potassium *t*-butoxide proved effective,



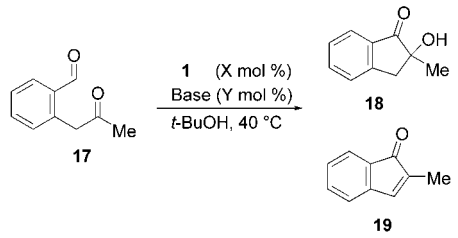
Scheme 6.



Scheme 7.



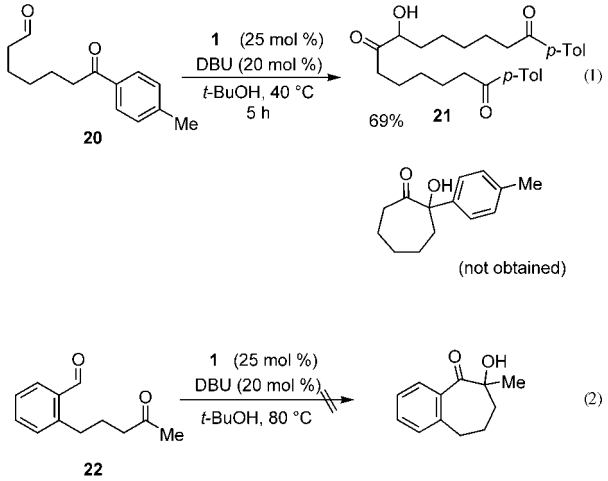
Scheme 8.



Scheme 9.

Table 3. Reaction of keto-aldehyde **17**.

Entry	X [mol %]	Base (Y [mol %])	Time [h]	Yield [%]	
				18	**19**
1	25	DBU (20)	9	59	14
2	25	*t*-BuOK (20)	6	54	7
3	50	*t*-BuOK (40)	1	73	5



Scheme 10.

although the reaction with triethylamine required a significantly longer reaction time (Entry 3). *t*-BuOH and THF were found to be the preferred solvents (Entries 2, 5–7). The use of lower catalyst loadings (25 mol % **1** and 20 mol % DBU) permitted a clean reaction to provide **7** in optimal yield (Entry 8).

Encouraged by these results, the formation of six-membered rings from other simple keto-aldehydes was examined. Keto-aldehyde **9** cyclized in 42% yield under these conditions to give the expected six-membered ring ketone **10** (Scheme 6). The reaction of other simple keto-aldehydes, however, proved to be capricious. For example, substrate **11** underwent cyclization in only 21% yield, and the dimeric benzoin adduct **13** was obtained as the major product (Scheme 7).

Fortunately, the use of more complex substrates proved feasible. Keto-aldehyde **14** derived from cholesterol[12] gave ketol **15** in moderate yield with high stereoselectivity (Scheme 8). Aldol **16** was obtained in 5% yield. It should also be noted that the potentially sensitive β-hydroxyketone moiety in the substrate remained intact under these conditions.

This reaction was highly stereoselective, a feature rationalized by the steric repulsion of the activated aldehyde and the 19-methyl group adjacent to the ketone. The relative stereochemistry was determined by comparison of the spectroscopic data of 3-*O*-acetyl derivatives of **15β** and **15α** with those of the reported compounds.[13]

Five-membered ring formation was achieved with keto-aldehyde **17**[14] (Scheme 9, Table 3). The initially disappointing yield, due to the formation of elimination product **19**, could be overcome by employing *t*-BuOK as the base in place of DBU, although increased catalyst loadings were needed to attain a rapid and clean reaction (Entries 2 and 3).

Two attempts to make larger rings were met with frustration. Aldehyde **20** gave only homo-coupled product **21** in 69% yield [Scheme 10, Eq. (1)]. Keto-aldehyde **22** provided neither the desired product nor the homo-coupled product, even at higher temperature.

Although the intramolecular ketone–aldehyde benzoin-forming reaction is not without its limitations, the mild reaction conditions, tolerance of sensitive functionalities (including β-hydroxy ketones), operational simplicity, and commercially available catalysts render this process an attractive means of carbon–carbon bond formation for the synthesis of complex molecules. Furthermore, given the long history of this process, including extensive mechanistic studies, it is remarkable that the use of ketones as electrophiles has not been exploited prior to our work.[16]

Experimental Section

Typical Procedure for the Benzoin-Forming Reaction

***2-Hydroxy-2-methyl-3,4-dihydro-2H-naphthalen-1-one* (7):** To a solution of keto-aldehyde **6** (104 mg, 0.590 mmol) in *t*-BuOH (4.5 mL) was added thiazolium salt **1** (37.5 mg, 0.149 mmol), and the temperature was raised to 40 °C. To the resulting suspension was added DBU (18.0 mg, 0.118 mmol) in *t*-BuOH (1.5 mL) at this temperature, and stirring was continued for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution, and the products were extracted with EtOAc ($\times 3$). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 72/28) to afford product **7** as a colorless oil; yield: 92.3 mg (89%); ^{1}H NMR ($CDCl_3$): $\delta = 8.04$ (d, 1H, $J =$ 8.0 Hz), 7.52 (dd, 1H, $J = 7.7$, 7.5 Hz), 7.35 (dd, 1H, $J = 7.7$, 8.0 Hz), 7.26 (d, 1H, $J = 7.5$ Hz), 3.87 (s, 1H), 2.97–3.18 (m, 2H), 2.17–2.31 (m, 2H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 201.8, 143.4, 134.0, 129.9, 129.0, 128.0, 126.9, 73.6, 35.8, 26.8, 23.9; IR (neat): $\nu = 3489$, 3066, 2972, 2933, 2864, 1689, 1603, 1455, 1371, 1290, 1222, 1155, 1097, 971, 796, 742 cm^{-1}.[15]

Supplementary Information

General experimental conditions, preparation and characterization of compounds **4**, **10**, **12**, **15**, and **18**.

Acknowledgements

Partial financial support by 21st Century COE program is gratefully acknowledged.

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[10] An extensive literature search has uncovered a single example of a benzoin-type reaction employing ketone electrophiles, namely the decarboxylative cyclization of 2,6-dioxoheptanoic acid cited in: H. Dugas, *Bioorganic Chemistry*, 3rd edn., Springer, New York, **1996**, p. 568.
[11] We have made preliminary efforts to establish the role of a retro-aldol-benzoin processes as a key pathway for the apparent preference of intramolecular benzoin-type reactions over the corresponding aldol. So far, these experiments have been inconclusive. For example, treatment of aldol **5** under typical benzoin-forming reaction conditions gave the elimination product (4%) and the recovered aldol adduct (94%).
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[16] After submission of this paper, we were informed of an independent, related by Enders et al. [*Synlett*, submitted]. We thank Professor Dieter Enders for the kind information.

