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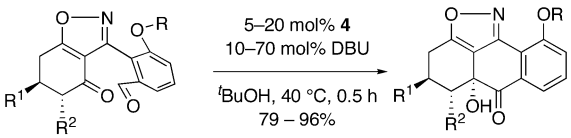
Catalytic Intramolecular Crossed Aldehyde−Ketone Benzoin Reactions: A Novel Synthesis of Functionalized Preanthraquinones

Yoshifumi Hachisu, Jeffrey W. Bode, and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology and CREST, Japan Science and Technology Corporation, O-okayama, Meguro-Ku, Tokyo 152-8551, Japan

Received March 25, 2003; E-mail: ksuzuki@chem.titech.ac.jp

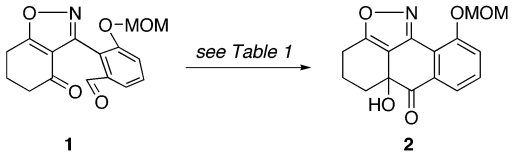
Chemical methods for the stereocontrolled synthesis of fused-ring polyacetates currently lag far behind recent innovations in the assembly of their macrocyclic counterparts.[1] Thus, despite the important and potent biological activities of these natural products, which count the tetracyclines[2] and angucyclines[3] as prominent members, few general approaches to their preparation currently exist. The construction of these sophisticated molecular architectures demands not only stereocontrolled introduction of key functionalities but also efficient fusion of complex, aromatic frameworks.[4] To address these challenges, we now report a novel, remarkably facile route to stereochemically defined preanthraquinones[5] via catalytic, intramolecular crossed aldehyde−ketone benzoin reactions. In addition to providing a useful and regiocontrolled synthesis of functionalized polycycles, this discovery also establishes a previously unexploited reaction mode for carbon−carbon bond formation under exceptionally mild conditions (eq 1).



(1)

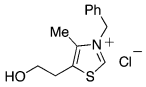
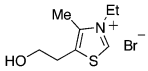
The basis for our approach is the ready accessibility of highly functionalized isoxazoles, such as **1**, by base-promoted cyclocondensations.[6,7] Recent studies from our laboratories have demonstrated the power of carbonyl coupling reactions for the stereocontrolled synthesis of complex polycyclic natural products,[8] and we reasoned that an efficient protocol to form a carbon−carbon bond between the carbonyl moieties of **1** would offer a regio- and potentially stereoselective preparation of preanthraquinones. Although acyl anion equivalents,[9c] including dithianes, or reductive couplings would exhibit the desired reactivity, we sought a simple, single-step solution and recognized that a benzoin-type reaction manifold would avoid superfluous substrate activation and manipulation steps. We approached this with some trepidation, however, as we were unaware of precedent for crossed aldehyde−ketone benzoin reactions, and few intramolecular examples have been reported.[9,10] Furthermore, given the reversible nature of the benzoin reaction, it was unclear if the desired cyclized product would be thermodynamically favored.

Using keto-aldehyde **1** as a model substrate, we investigated conditions for intramolecular, aldehyde−ketone couplings (eq 2). Initial attempts to employ a classical cyanide-catalyzed procedure (Table 1, entry 1) were unfruitful; however, traces of the desired product could be obtained by performing the reaction in DMF (entry 2). Progress was achieved by utilizing thiazolium salt **3** (entry 3),[11] which produced tetracycle **2** in synthetically useful yields. Further investigations revealed the advantages of commercially available thiazolium salt **4** and identified tBuOH as the preferred solvent (entries 4−6). Although a variety of tertiary amine bases were effective, the use of catalytic DBU permitted lower reaction temperatures (40 °C), shorter reaction times (30 min), and optimal yields of **2** (95% yield, entry 7). High dilution was not necessary for clean reaction, and lower catalyst loadings (5 mol % **4**, 10 mol % DBU) were equally efficient (Table 1, entry 8). Using these mild and convenient reaction conditions, we obtained products in high yield and free of byproducts; the anticipated dimeric benzoin side-products were not observed.



1 **2** (2)

Table 1. Optimization of Reaction Conditions for Catalytic, Intramolecular Benzoin Reactions[a]

entry	catalyst	base	solvent	temp (°C)	time (h)	yield[b] (%)
1	NaCN[c]	—	EtOH	80	44	0
2			DMF	45	18	22
3	 **3**[d]	Et_3N	EtOH	80	11	79
4		Et_3N	EtOH	80	4	88
5	 **4**[d]	Et_3N	DMF	80	18	46
6		Et_3N	tBuOH	80	3	90
7		DBU	tBuOH	40	0.5	95
8		DBU	tBuOH	40	0.5	94[e]

[a] Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale at 0.05 M. [b] Yield refers to the chemical yield of isolated, analytically pure products. [c] 30 mol % NaCN. [d] Thiazolium salt (20 mol %) and base (70 mol %) were employed. [e] DBU (10 mol %) and **4** (5 mol %) at 0.1 M were employed.

A key feature of this methodology is the excellent diastereoselectivity observed with substrates possessing additional stereogenic centers (Table 2, entries 3−4), providing products uniquely functionalized for further elaboration about the preanthraquinone ring. Chiral keto-aldehyde **7** afforded tertiary alcohol **8** as a >20:1 ratio of stereoisomers (entry 3). Notably, an acidic and enolizable β-ketoester moiety in **9** did not interfere with the cyclization nor lead to elimination or retro-aldol products of the resulting β-hydroxy ester in **10** (entry 4). Exocyclic ketones **11** and **13** provided naphthoquinone precursors **12** and **14** in excellent yield (entries 5 and 6).

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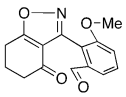
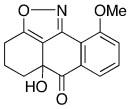
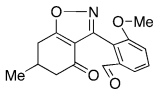
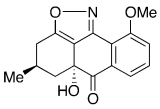
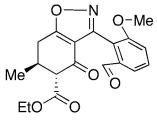
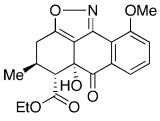
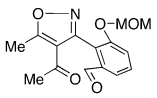
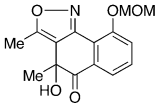
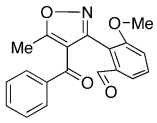
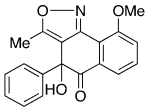
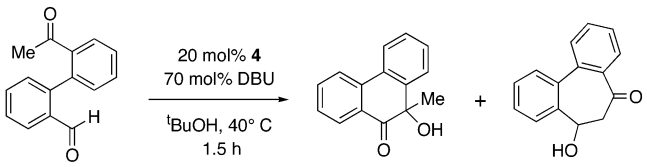
Table 2. Intramolecular Aldehyde−Ketone Benzoin Reactions[a]

entry	keto-aldehyde	product	diastereomer ratio	yield[b] (%)
1	 **5**	 **6**	—	95
2			—	95[c]
3	 **7**	 **8**	>20:1[d,e]	90
4	 **9**	 **10**	>20:1[d,f]	79
5	 **11**	 **12**	—	96
6	 **13**	 **14**	—	94

[a] Unless otherwise indicated, all reactions were performed at 0.05 M in ^{t}BuOH at 40 °C for 0.5 h using 20 mol % **4** and 70 mol % DBU. [b] Yield refers to the chemical yield of isolated, analytically pure products. [c] This reaction was performed at 0.1 M using 5 mol % **4** and 10 mol % DBU. [d] Determined by ^{1}H NMR analysis of the unpurified reaction products. For comparison, the other stereoisomer was obtained under alternative reaction conditions. [e] Relative stereochemistry assigned by analogy to **10**. [f] Structure determined by X-ray analysis.

The isoxazole moiety serves as a convenient masking group for the synthesis of anthraquinoid structures; however, it is not a prerequisite for the crossed benzoin reaction, and keto-aldehyde **15** gave benzoin product **16** in good yield, albeit in competition with intramolecular aldol product **17** (Scheme 1).[12]

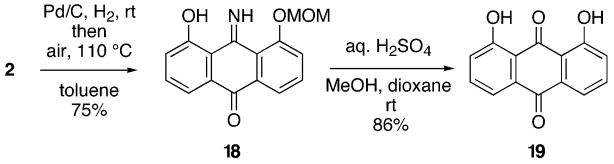
Scheme 1



15 **16** 65% **17** 26%

Although we expect the full potential of this reaction to be realized in its application to stereochemically elaborate polycyclic compounds, the ease of starting material preparation, rapid reaction times, and complete regiocontrol already offer a useful protocol for the synthesis of functionalized anthraquinones. Benzoin product **2** was readily converted to imino-anthraquinone **18** by a one-pot procedure simply by treatment with Pd/C in a hydrogen atmosphere followed by in situ Pd-catalyzed oxidation in air (Scheme 2).

Scheme 2



18 **19**

Hydrolysis of **18** afforded dantron (**19**), which was in all respects identical to an authentic sample.

In conclusion, we have reported a novel approach to the synthesis of stereodefined preanthraquinones via the first crossed aldehyde−ketone benzoin reaction. This process offers a simple and remarkably mild entry to useful, orthogonally protected polycyclic quinones with a high degree of regio- and stereoselectivity. The discovery that ketones can serve as electrophiles for benzoin-type processes opens new pathways for the development of catalytic, stereoselective reactions.[13,14]

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Supporting Information Available: Experimental procedures and characterization for benzoin products and X-ray crystallographic data for **10** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) At the current stage of development, we have found this reaction to be viable for a variety of keto-aldehydes, including aliphatic systems. Further reaction development to exclude the competing aldol processes as well as mechanistic studies are underway and will be reported in due course.
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