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Aldol reactions of 1,2-diketones catalyzed by amines to afford furanose derivatives

Enukonda Jithender, Isamu Katsuyama, Dongxin Zhang, Sherida Johnson, Fujie Tanaka *

Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan

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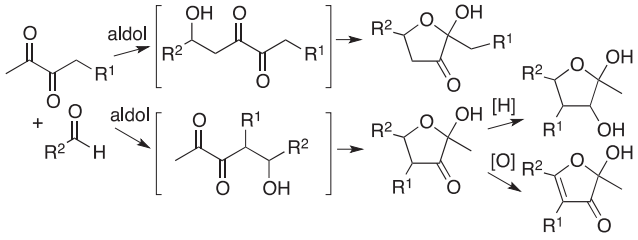
ABSTRACT

Molecules with furanose units are often bioactive. To concisely synthesize these molecules, we have developed aldol reactions of 1,2-diketones that afford furanose derivatives in one pot. For these reactions with the use of *N*,*N*′-diisopropylethylamine as catalyst, aldol products were obtained via C–C bond formation at the internal methylene carbon of the acetyl alkyl ketone derivatives. Regioselectivities of the reactions depended on the catalyst. The aldol products from the reactions with aldehydes in which the C–C bond formation occurred at the internal methylene carbon of the acetyl alkyl ketone derivatives were easily air-oxidized to afford the corresponding 2-hydroxy-2*H*-furanone derivatives.

Furanose derivatives are important molecules as they are found in biomolecules (such as DNA and RNA) and in bioactive natural products.[1,2] To access furanose derivatives, we designed a route involving aldol reactions of 1,2-diketones (Scheme 1). The 1,2-diketones are expected to be useful synthons because they act as both nucleophiles (such as enolates and enamines) and electrophiles.[3,4] However, control of the reactivity of 1,2-diketones is difficult; reactions with 1,2-diketones may result in the formation of undesired polymerized products.[3,4] Because of the difficulty of the reactions of 1,2-diketones as nucleophiles (as in situ-formed enolates and enamines), there are no reports on aldol reactions of acyclic 1,2-diketones in which the 1,2-diketones act as nucleophiles.[3,4] In addition, when the 1,2-diketones are not symmetric, their reactions may generate a mixture of regioisomers. To utilize the aldol route for the synthesis of furanose derivatives, it is necessary to develop ways to control the reactions of 1,2-diketones. Here we report initial results toward the development of the aldol methods using 1,2-diketones as starting materials to access substituted furanose derivatives.

First, catalysts and conditions were searched for aldol reactions of 2,3-pentanedione (**1**) with 4-nitrobenzaldehyde (**2a**) and with 4-cyanobenzaldehyde (**2b**). We tested various amines as catalysts.[5–7] Amines tested for the reactions included primary, secondary, and tertiary amines and amine-derived bases; they were used without or with acids. Selected results are shown in Table 1. Basic conditions gave aldol products **3** in varied yields with little or no



Scheme 1. Aldol reactions of 1,2-diketones to synthesize furanose derivatives.

formation of **4**. In contrast, some amine-acid conditions gave **4** with **3** in varied ratios and yields. Amino acids, including proline, were not effective catalysts for the formation of aldol products **3** or **4** under the conditions tested including those in DMSO.

Among those tested, reactions using *N*,*N*′-diisopropylethylamine (DIPEA, $i\mathrm{Pr_2NEt}$) as catalyst[6] were the best to give aldol product **3** in good or reasonable yields at room temperature (25 °C) (entries 3 and 6). To obtain aldol product **4** as the major product over the regio isomer **3**, conditions using pyrrolidine–acetic acid catalysis[7] were the best among those tested, although the yields of the aldol product **4** were moderate (entries 7 and 8). Under the pyrrolidine–acetic acid catalysis conditions, self-reactions of 2,3-pentanedione were observed, and this caused the relatively low yields of the cross aldol products.

For the formation of aldol product **3**, the C–C bond formation occurred at the substituted methylene carbon (i.e., at the 4-position)

* Corresponding author.
E-mail address: ftanaka@oist.jp (F. Tanaka).

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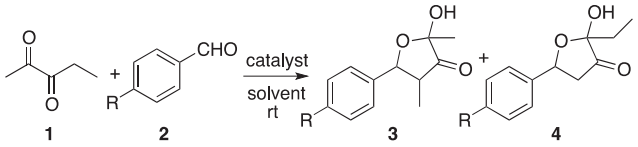
Table 1
Selected conditions and catalysts for aldol reactions of 2,3-pentanedione[a]



Entry	R	Catalyst/solvent, time	**3** and/or **4**	Yield[b] (%)
1	NO_2	Pyrrolidine/DMSO, 20 h	**3** only[c]	40 (**3aa**)
2	NO_2	Prolinamide/DMSO, 48 h	**3** only[c]	42 (**3aa**)
3	NO_2	iPr$_2$NEt/DMSO, 14 h	**3** only[c]	60 (**3aa**)
4	NO_2	DABCO/DMSO, 20 h	**3** only[c]	58 (**3aa**)
5	CN	Prolinamide/DMSO, 48 h	**3** only[c]	30 (**3ab**)
6	CN	iPr$_2$NEt/DMSO, 14 h	**3** only[c]	48 (**3ab**)
7	CN	Pyrrolidine–acetic acid (1:1)/THF, 48 h	**3**:**4** = 1:4[d]	21 (**4ab**)
8	CN	Pyrrolidine–acetic acid (1:1)/DME, 72 h	**3**:**4** = 1:9[d]	17 (**4ab**)

[a] Conditions: 2,3-pentanedione (**1**) (1.0 mmol for entries 1–6, 1.3 mmol for entries 7 and 8), aldehyde **2** (1.0 mmol), and catalyst (0.2 mmol) in solvent (1.0 mL) at room temperature (25 °C). Aldol products **3** and **4** were separately purified.
[b] Isolated yield of the compound in the parenthesis.
[c] Analyzed by TLC.
[d] Determined by ^{1}H NMR.

of 2,3-pentanedione. To generate aldol product **4**, the methyl group (i.e., at the 1-position) of 2,3-pentanedione was the reaction site of the C–C bond formation.

Under the DIPEA catalysis conditions, formation of the product may be controlled thermodynamically. That is, within possible enolates **A** and **B**, enolate **B** should be more favorably present than enolate **A**, and the major enolate **B** should be used for the C–C bond formation to lead product **3** (Fig. 1). On the other hand, under the pyrrolidine–acetic acid catalysis conditions, enamine **C** may be favorably formed compared to enamines **D** and **E** because of sterical reasons, and the reaction of enamine **C** results in the formation of product **4** (Fig. 1). Alternatively, regardless of the presenting ratios of enamines **C**, **D**, and **E**, less-hindered enamine **C** may be preferentially used for the C–C bond formation because enamine **C** leads less-hindered transition state for the C–C bond formation compared to other enamines.

Next, aldol reactions of various 1,2-diketones (acetyl alkyl ketones) with arylaldehydes were performed using the DIPEA catalysis conditions to afford various aldol products **3** (Scheme 2). For these reactions, the products were generated from the C–C bond formation at the internal methylene carbon. The relationship between the aryl group (Ar) and R group in the major isomers was determined to be *trans* based on the coupling constant J values in the ^{1}H NMR. The *trans*-relationship may be the result of the isomerization at the carbonyl α-position of the products to give thermodynamically stable stereoisomers.

The DIPEA catalysis conditions were useful to give the aldol products in the reactions with benzaldehydes bearing electron-withdrawing substituents (such as NO_2 and CN) and with 4-pyridinealdehyde. For the reactions with benzaldehydes without electron-withdrawing substituents, however, the cross aldol

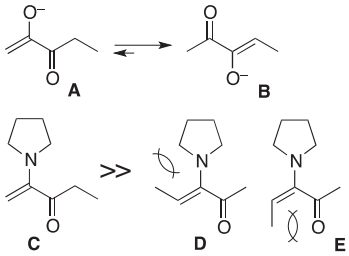
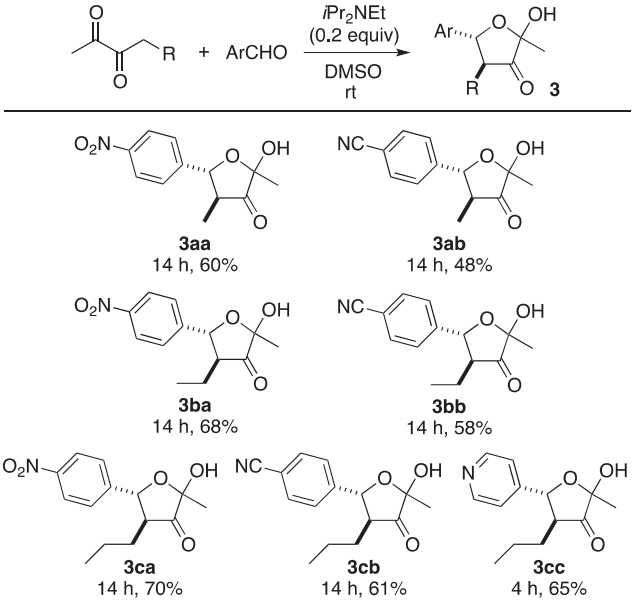


Figure 1. Enolates and enamines of the 2,3-pentanedione.



Scheme 2. Aldol reactions of 1,2-diketones with arylaldehydes catalyzed by *N*,*N*′-diisopropylethylamine (DIPEA). Reagents and conditions: 1,2-diketone (1.0 mmol), ArCHO (1.0 mmol), and iPr$_2$NEt (0.2 mmol) in DMSO (1.0 mL) at 25 °C. Yields of **3aa** and **3ab** are also included in Table 1.

products were not obtained in reasonable yields. Self-condensations including polymerization of 1,2-diketones occurred significantly over the desired cross-aldol reaction.

When isatin was used as the electrophile (acceptor) of the reaction under the DIPEA catalysis conditions, a mixture of **5** and **6** was obtained. In these cases, the C–C bond formation occurred at either the methyl carbon or the internal methylene carbon (Scheme 3). For the formation of **6a**, enolate **A** (Fig. 1) was involved, while enolate **B** led to the formation of **5a**. The steric bulk of the oxindole moiety may be the reason for the formation of a mixture of regio isomers. Although the reactions with isatin were not regioselective, spirooxindole furanose derivatives[8] were obtained in one pot.

The pyrrolidine–acetic acid conditions were also used for aldol reactions of a C7 1,2-diketone, 2,3-heptanedione (Scheme 4). In these reactions, the major aldol products were generated from the C–C bond formation at the methyl carbon regardless of the acceptor reactants.