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Base-Controlled Reactions through an Aldol Intermediate Formed between 2-Oxoaldehydes and Malonate Half Esters

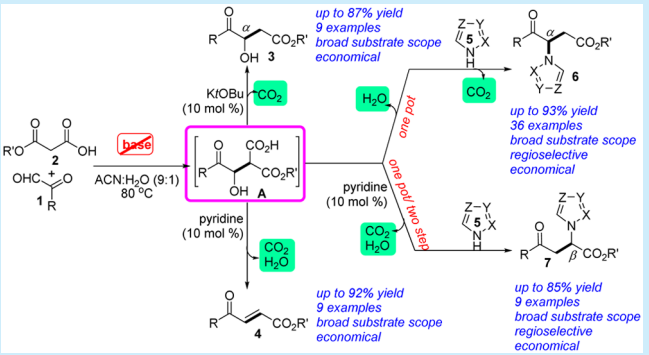
Atul Kumar,[†,‡] Shahnawaz Khan,[†,‡] and Qazi Naveed Ahmed*[,†,‡]

[†]Medicinal Chemistry Division, Indian Institute of Integrative Medicine (IIIM), Jammu 180001, India

[‡]Academy of Scientific and Innovative Research (AcSIR-IIIM), Jammu 180001, India

Supporting Information

ABSTRACT: A practical, atom-economical, base-directed, and highly efficient method for the generation of different selective products through a common aldol intermediate of 2-oxoaldehydes and malonate half esters is successfully developed. The addition of a strong basic environment (potassium *tert*-butoxide) catalyzed the synthesis of stable decarboxylative aldol products (α-hydroxy ketones), while the Doebner modification procedure resulted in decarboxylative elimination to (*E*)-α,β-unsaturated esters in good yields. The application of this method in one pot and one pot/two steps with azoles helped to develop regioselective α- and β-azolated products in appreciable yields.



Inspired by Nature, which uses carboxylic acids/carbonates as antecedents to carbon nucleophiles in a variety of reactions, synthetic chemists have imitated this process to perform a different decarboxylative carbon−carbon bond formation using a variety of substrates.[1] One among these utilized malonate half esters as simple ester surrogates.[2] In the past, different metal, base/organocatalyzed reactions have been established in which malonate half esters and related species undergo decarboxylation and coupling with carbonyl electrophiles.[3] However, the condensation reaction is not feasible in the absence of a promoter. As an exception, it is a well-established fact that in 2-oxoaldehydes (OAs) the higher reactivity of the aldehydic group in comparison to normal aldehydes is attributed to the existence of an electron-withdrawing ketone group and has been well explored to produce different important structures.[4] This highlights a distinct feature of OAs that led to the generation of selective products through base-controlled reactivity of the aldol intermediate formed between 2-oxoaldehydes and malonate half esters (Figure 1a). Previously, different groups have established the synthesis of α,β-unsaturated esters using different carbon−carbon bond-forming strategies.[5] Typically, the transformation is realized via the Wittig reaction/Meyer−Schuster rearrangement or Horner−Wadsworth−Emmons method.[6] A significant drawback of these methods is their modest atom economy and use of expensive substrates. In addition, the aza-Michael addition of azoles to α,β-unsaturated carbonyl compounds for the generation of β-azolated structures is a well-explored reaction (Figure 1b).[7] However, selective synthesis of α-azolated product is still a challenge. In this regard, the malonate half esters proved to be the substrate of choice for OAs. Besides being an inexpensive reactant, the reactions are highly atom-economical, and the common aldol intermediate

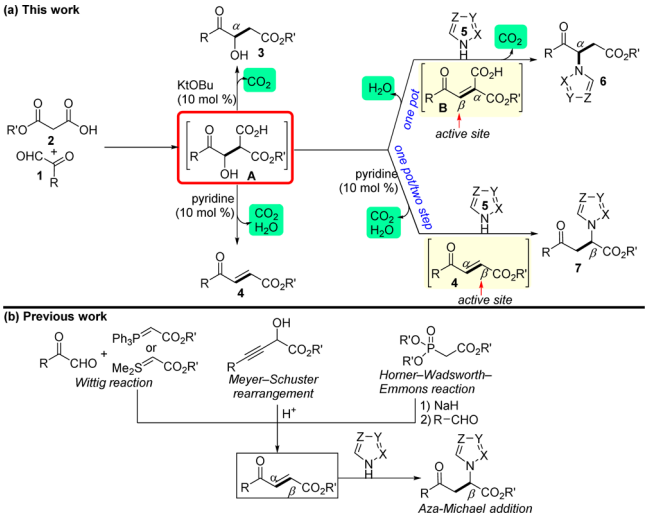


Figure 1. Summary of this work.

produced under base-free conditions could be helpful to selectively generate different valuable products in good yields.[8] Beyond the synthesis of (*E*)-α,β-unsaturated esters under the Doebner modification procedure,[9] α-hydroxy ketones were produced selectively in good yields when stirred with 0.1 mmol of K*t*OBu. The salient feature of the reaction is its control for the selective generation of α- and β-azolated product in one pot. The selectivity in azolation reactions could be justified through the involvement of intermediates **B** and **5**, respectively.

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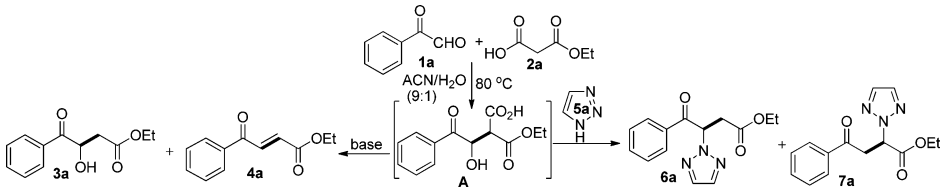
Table 1. Optimization of the Reaction



					yields[e] (%)			
entry	**1a** (mmol)	**2a** (mmol)	base/**5a** (mmol)	time (h)	**3a**	**4a**	**6a**	**7a**
1	1	1	**5a** (0.1)	4	13	17	37	24
2	1	1	nBuLi (0.1)	4	74	15		
3	1	1	TEA (0.1)	4	67	18		
4	1	1	DIPEA (0.1)	4	68	20		
5	1	1	KOH (0.1)	4	62	33		
6	1	1	DBU (0.1)	4	69	23		
7	1	1	K*t*OBu (0.1)	4	76	10		
8[a]	**1.1**	**1**	**K*t*OBu (0.1)**	**4**	**87**	**7**		
9	1.2	1	K*t*OBu (0.1)	4	86	8		
10	1	1	pyridine (0.1)	6	15	82		
11[b]	**1.1**	**1**	**pyridine (0.1)**	**6**	**5**	**92**		
12[c]	**1.1**	**1**	**5a (1)**	**12**	-	**10**	**89**	**traces**
13[d]	**1.1**	**1**	**pyridine (0.1) and 5a (1)**	**8**		**7**		**83**

[a]Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), and K*t*OBu (0.1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 4 h; [b]Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), and pyridine (0.1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 4 h. [c]Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), and 1*H*-1,2,3-triazole **5a** (1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 12 h; [d]Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), and pyridine (0.1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 4 h followed by **5a** (1 mmol) for another 4 h; [e]Isolated yields.

In our preliminary investigation, we aspire to study the nature of the products obtained by reacting phenylglyoxal **1a** (1 mmol), 3-ethoxy-3-oxopropanoic acid **2a** (1 mmol), and 0.1 mmol of **5a** in 1 mL of ACN/H_2O (9:1) at 80 °C (entry 1, Table 1). In this reaction, we isolated a mixture of four products **3a** (13%), **4a** (17%), **6a** (37%), and **7a** (24%) after 4 h. To our delight, the reaction produced an unexpected α-azolated product **6a** in moderate yields. In order to attain better yields and selectivity of each product, a preliminary set of reactions through an aldol intermediate **A** (produced between **1a** and **2a** under base free condition at 80 °C) under a different set of conditions have been carried out (entries 2−13). Primarily, the intermediate **A**, generated in situ between **1a** (1 mmol) and **2a** (1 mmol) at 80 °C in ACN/H_2O (9:1) for 2 h, was screened against different bases (entries 2−7). We observed that the ethyl (*R*)-3-hydroxy-4-oxo-4-phenylbutanoate **3a** was produced exclusively in 76% yield for 4 h when the reaction was conducted with 0.1 mmol of K*t*OBu (entry 7, Table 1). Screening of our reaction at different concentrations of **1a** against **2a** was also performed (entries 8 and 9). We observed that a better yield of desired product **3a** was observed with 1.1 mmol of phenylglyoxal (entry 8, Table 1). Further reactions performed under the Doebner modification procedure resulted in the selective synthesis of ethyl (*E*)-4-oxo-4−phenylbut-2-enoate **4a** in good yield (entries 10 and 11). However, the best yields were obtained when **1a** (1.1 mmol) was initially stirred with **2a** (1 mmol) in ACN/H_2O (9:1) for 2 h followed by the addition of pyridine (0.1 mmol) and stirring at the same temperature for 4 h (entry 11). Next, two different reactions were monitored with 1*H*-1,2,3-triazole **5a** in equivalence mode at 80 °C in ACN/H_2O (9:1) against intermediate **A** in one-pot and one-pot/two-step strategies (entries 12 and 13). The reaction of intermediate **A** with **5a** (1 mmol) in one pot generated exclusively α-azolated product **6a** in 89% yield (entry 12). Finally, as observed, the optimal reaction conditions for the selective synthesis of β-azolated product turned out to be phenylglyoxal **1a** (1.1 mmol), malonate half ester **2a** (1 mmol), and pyridine (0.1 mmol) at 80 °C in ACN/H_2O (9:1) for 4 h followed by stirring for additional 4 h with **5a** (83%, entry 13).

Having observed that K*t*OBu and pyridine independently catalyzed the decarboxylative addition of malonate half esters **2** with 2-oxoaldehyde **1** for the selective synthesis of α-hydroxy ketones **3** and (*E*)-α,β-unsaturated esters **4**, respectively, we then decided to examine the substrate scope of each method. As compiled in Scheme 1, primarily a variety of 2-oxoaldehydes **1** were tested against 3-ethoxy-3-oxopropanoic acid **2a** under the K*t*OBu environment (entries **3a**−**g**). We were pleased to find that in all tested reactions the desired products **3** were produced in good yields (74−87%). Besides monosubstituted OAs, the disubstituted and heteroaromatic substrates were also compatible with the reaction condition (entries **3f** and **3g**). In addition, different experiments were performed between 3-methoxy-3-oxopropanoic acid **2b** and phenylglyoxal **1** (entries **3h** and **3i**). In this case as well, yields were good for all the reactions conducted. In general, we observed that irrespective of the nature of OAs and malonate half esters, all of the tested reactions were efficiently transformed to **3** within 4 h. Furthermore, to check the substrate scope of the decarboxylative elimination reaction for the generation of **4**, we conducted different reactions between half malonate esters **2** and 2-oxoaldehydes **1** (entries **4a**−**4i**). It was observed that both electron-rich and electron-deficient OAs could be smoothly transformed into the desired product when treated with **2a** for 6 h. The reaction was compatible with naphthyl and thiophene based OAs, as well (entries **4g** and **4h**). In addition, the reaction of 4-methylphenylglyoxal with **2b** also generated good yields of the desired product (entry **4i**).

In continuation, different sets of reactions for the synthesis of novel α-azolated products **6** were performed as per the optimized

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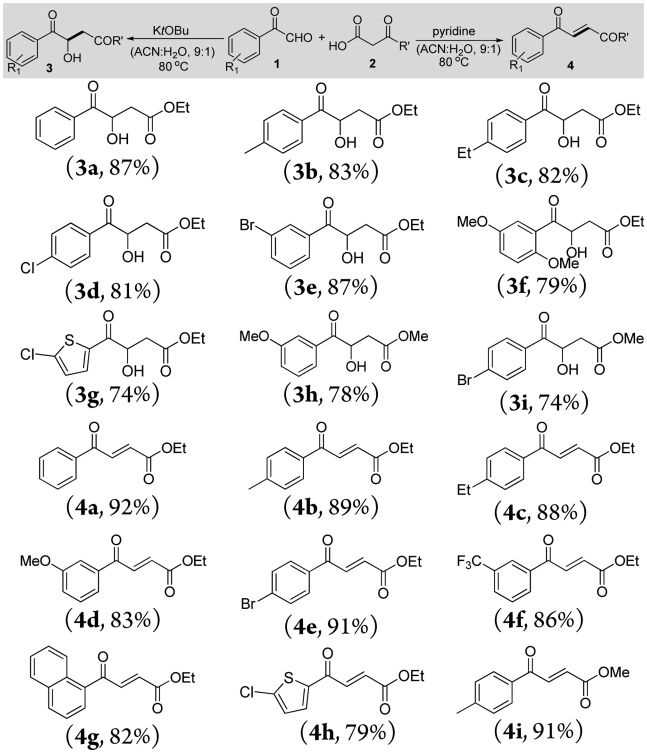
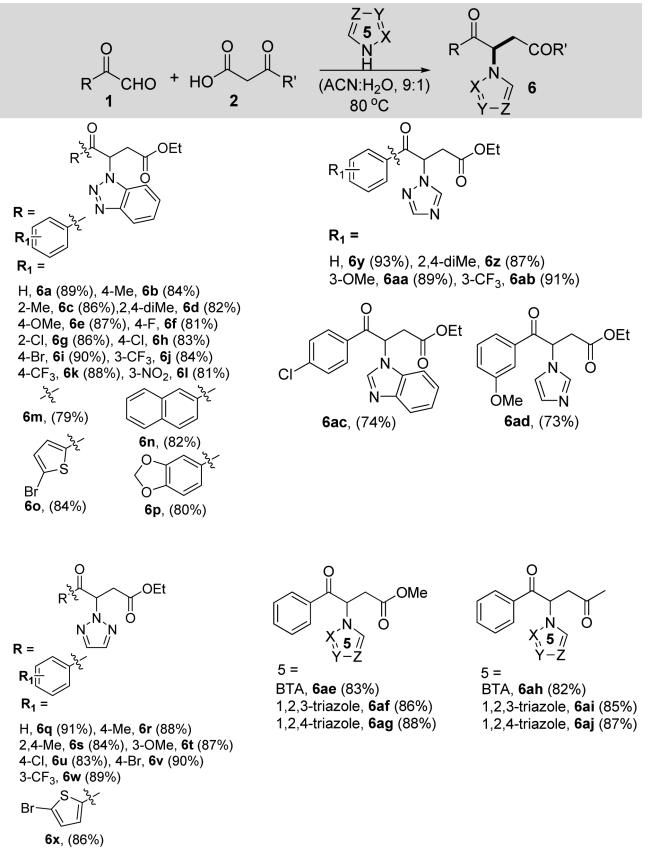
Scheme 1. Scope of Decarboxylative Condensation Reaction[a]



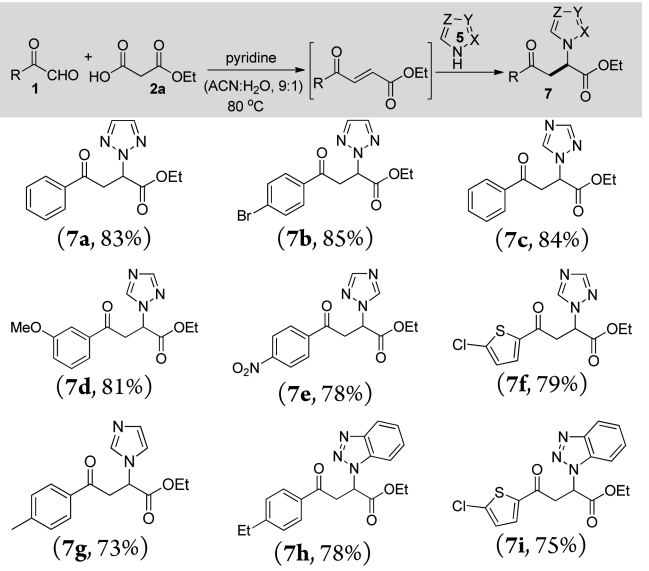
[a]Reaction conditions: for the synthesis of **3**, **1** (1.1 mmol), **2** (1 mmol), and K*t*OBu (0.1 mmol) in 1 mL ACN/H_2O (9:1) at 80 °C for 4 h; for the synthesis of **4**, **1** (1.1 mmol), **2** (1 mmol), and pyridine (0.1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 6 h.

Scheme 2. Scope of One-Pot α-Azolation Reaction[a]



[a]Reaction conditions: **1** (1.1 mmol), **2** (1 mmol), and **5** (1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 12 h.

Scheme 3. Scope of One-Pot/Two-Step β-Azolation Reaction[a]



[a]Reaction conditions: **1** (1.1 mmol), **2a** (1 mmol), and pyridine (0.1 mmol) in 1 mL of ACN/H_2O (9:1) at 80 °C for 4 h followed by stirring with **5** (1 mmol) for another 4 h.

conditions mentioned in entry 12, Table 1 (Scheme 2). In one set, we evaluated the reaction of malonate half ester **2a** and benzotriazole (BTA) with a diverse set of OAs (entries **6a−p**). Both electron-rich and electron-deficient aryl-substituted OAs could be smoothly transformed into the desired products. Furthermore, substituents at different positions of the aryl ring (para, meta, and ortho position) do not affect the efficiency. In addition, methyl-, naphthyl-, heteroaromatic-, and 3,4-methylenedioxy-substituted OAs were also tolerant in this transformation (entries **6m−p**). Another set of reactions was performed between **2a**, 1*H*-1,2,3-triazole **5a**, and OAs **1** (entries **6q−x**). In all of the reactions tested, the desired products were isolated in good yields with complete selectivity despite the nature of the OAs used. In addition, a few experiments were conducted with different azoles as well (entries **6y−ad**). It was clearly observed that the nature of the phenyl ring in 2-oxoaldehyde and azoles has no appreciable effect on the reaction and its yields. We also observed that the conversion to its corresponding α-azolated products **6** with 3-methoxy-3-oxopropanoic acid **2b** and 1,3-diones were very smooth and produced good yields (entries **6ae−aj**).

The scope of our method was further extended in establishing different one-pot/two-step methods for the selective synthesis of β-azolated products **7** as described in entry 13, Table 1 (Scheme 3). In these experiments, we observed that both electron-rich and electron-deficient OAs produced desired products in good yields (entries **7a−i**). Furthermore, substituents at different positions of the arene group and their electronic nature do not affect the efficiency of the reaction. Both phenylic and heterocyclic substrates could afford the corresponding product in moderate to good yields (73−85%).

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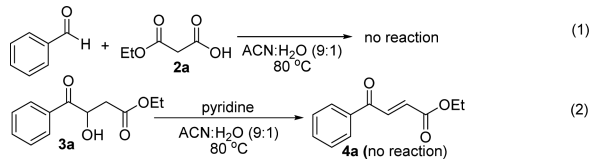
In order to justify the mechanism of these reactions, we performed a few controlled experiments (Scheme 4). In

Scheme 4. Control Experiments



experiment 1, the reaction of benzaldehyde with 3-ethoxy-3-oxopropanoic acid **2a** at 80 °C failed to undergo any reaction, suggesting that 2-oxo group in OAs facilitated the reaction through a common aldol intermediate **A**. In addition, α-hydroxy ketone **3a** was found to be stable in ACN/H_2O when heated with 0.1 mmol of pyridine at 80 °C for 6 h. These two experiments and literature precedent justifies that the synthesis of **3** involves decarboxylation pathway, whereas the generation of **4** is understood as a decarboxylative elimination reaction.[10,6a] Furthermore, α-azolation follows initial dehydration to **B** followed by β-azolation to final product **6**. In addition, the β-azolation is well understood to proceed through intermediate **4**.[11]

In summary, we demonstrated base-controlled, simple, economical, efficient approaches for the selective generation of different valuable structures. These protocols provided a broad scope of the desired products in good yields. Furthermore, applications across different nucleophiles for the generation of different α- and β-selective products are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02016.

General information, general procedure, procedures for control experiments, characterization data, and ^{1}H NMR and ^{13}C NMR spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: naqazi@iiim.ac.in.

ORCID

Qazi Naveed Ahmed: 0000-0002-6890-7587

Notes

The authors declare no competing financial interest.

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