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Stereoselective Synthesis of α-Ylidene-β-dicarbonyl Compounds: A Mild $PhI(OAc)_2$-mediated Dehydrogenation Process

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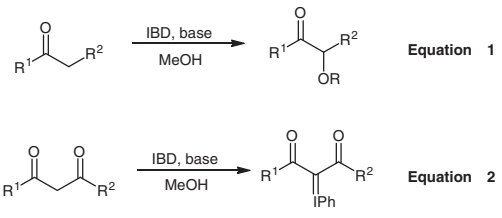
$PhI(OAc)_2$-mediated dehydrogenation of α-alkyl-β-dicarbonyl compound has been developed to afford α-ylidene-β-dicarbonyl compounds with high stereoselectivity under mild conditions. This process provides a complementary entry to stereoselectivity for the Knoevenagel reaction.

In recent years, hypervalent iodine reagents have played an increasingly important role in organic synthesis due to their low toxicity, high stability, and unique reactivities.[1] One of the important applications is to efficiently oxidize substrates with diverse functional groups.[2] Among these oxidations, α-functionalization of carbonyl compounds mediated by hypervalent aryl-λ^3-iodanes has been extensively investigated and has broad synthetic utility (Scheme 1).[3] $PhI(OAc)_2$ (IBD) can be employed as an oxidant to introduce an OR group (R = Ac, Me) into an α-position of carbonyl carbon from simple ketone compounds (eq 1).[3f,4] For instance, with β-dicarbonyl compounds, iodonium ylide is formed under similar conditions (eq 2).[5]

α-Ylidene-β-dicarbonyl compounds are versatile synthetic intermediates, and can be prepared through the Knoevenagel condensation of aldehydes/ketones and β-dicarbonyl compounds in general.[6] And the stereochemistry of newly formed double bond is mainly controlled by steric effects to yield thermodynamically stable *E*-isomer as major product.[7] Methods to obtain thermodynamically unstable *Z*-isomers have been rarely reported.[8] Herein we report a mild IBD-mediated dehydrogenation reaction of α-alkyl-β-dicarbonyl compounds, which could produce corresponding α-ylidene-β-dicarbonyl compounds (Scheme 2). The new process presented in this paper would afford different stereoselectivity.

The reaction was found when we tested the Pd-catalyzed dehydrogenation of α-ylidene-β-dicarbonyl compound **1a** by using IBD as oxidant[9] (Table 1, Entry 1).[10] To our surprise, **2a** was isolated in 15% yield as the major by-product. The elimination of H-atom in **1a** would result in the formation of compound **2a**. If it was true, additional base would be necessary to capture H-atom. Actually, the yield of **2a** was promoted in the presence of K_2CO_3 (Table 1, Entry 2). And after several attempts, we found that $Pd(OAc)_2$ was not involved into this transformation at all (Table 1. Entries 3–6). Without $PhI(OAc)_2$



Scheme 1. α-Functionalization of ketone and β-dicarbonyl compounds using IBD as oxidant.

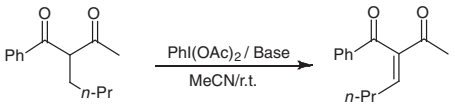
Scheme 2. IBD-mediated dehydrogenation reaction.

Table 1. Discovery journey of IBD-mediated dehydrogenation of **1a**

1a **2a**

Entry	$Pd(OAc)_2$ /equiv	$PhI(OAc)_2$ /equiv	K_2CO_3 /equiv	Yield /%
1	0.1	2.0		15
2	0.1	2.0	2.2	44
3	0.1	—	—	0
4	—	2.0	—	20
5	—	—	2.2	0
6	0.1	—	2.2	0
7	—	2.0	2.2	50

Table 2. Optimizing reaction conditions for $PhI(OAc)_2$-mediated dehydrogenation[a]



1b **2b**

Entry	$PhI(OAc)_2$ /equiv	Base (equiv)	Time /h	Yield[b] /%
1	0	K_2CO_3 (2.2)	72	0
2	1.1	K_2CO_3 (2.2)	72	29
3	2.0	K_2CO_3 (2.2)	8	58
4	2.0	K_2CO_3 (1.1)	72	70
5	2.0	Na_2CO_3 (2.2)	48	58
6	2.0	$NaHCO_3$ (2.2)	48	69
7	2.0	NaH (2.2)	24	56
8	2.0	Et_3N (2.2)	48	<5
9	2.0	DIPEA (2.2)	48	<5
10	2.0	$KHCO_3$ (2.2)	24	74
11	2.0	—	72	8[c]

[a]Reaction conditions: **1b** (0.3 mmol), MeCN (3 mL), r.t. [b]Isolated yield. [c]76% of **1b** was recovered.

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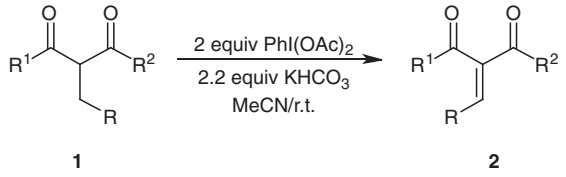
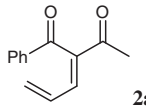
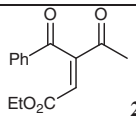
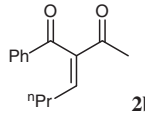
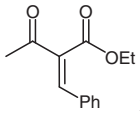
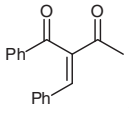
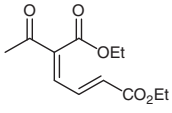
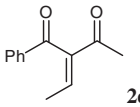
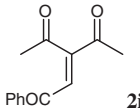
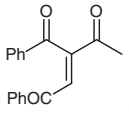
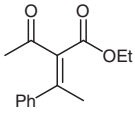
Table 3. Optimizing reaction conditions for $PhI(OAc)_2$-mediated dehydrogenation[a]



1 **2**

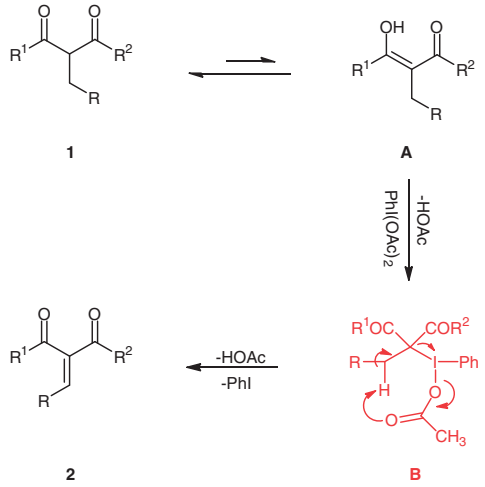
Entry	Product **2** Time/yield[a]; (*Z*):(*E*)[b]	Entry	Product **2** Time/yield[a]; (*Z*):(*E*)[b]
1	 **2a** 20 h/53%; (*Z*):(*E*) = 99:1	6	 **2f** 5 h/66%; (*Z*):(*E*) = 17:1
2	 **2b** 24 h/74%; (*Z*):(*E*) = 99:1	7	 **2g** 6 h/4%; (*Z*):(*E*) = 3:2
3	 **2c** 6 h/74%; (*Z*):(*E*) = 10:1	8	 **2h** 24 h/70%; (*Z*):(*E*) = 99:1
4	 **2d** 24 h/61%; (*Z*):(*E*) = 25:1	9	 **2i** 6 h/69%; (*Z*):(*E*) = —
5	 **2e** 5 h/51%; (*Z*):(*E*) = 6:1	10	 **2j** 48 h/<5%

[a]Isolated yield. [b]Estimated by ^{1}H NMR.

the reaction does not work (Table 1. Entries 3, 5, and 6). The results of $PhI(OAc)_2$-mediated transformation of a readily available substrate into α-ylidene-β-dicarbonyl compounds prompted us for further investigations (Table 1, Entry 7).

Initially, $PhI(OAc)_2$ dehydrogenation reaction was screened by using various bases, and the results were showed in Table 2. It was interesting to find that **1b** could be transferred to **2b** in good yield (74% isolated yield) by using $KHCO_3$ as the base together with $PhI(OAc)_2$. Other inorganic bases, such as K_2CO_3, Na_2CO_3, $NaHCO_3$, and NaH also could promote this reation, while organic bases, such as Et_3N and DIPEA gave lower yields. The yield is lower with the decrease of IBD (Table 2, Entries 1 and 2). The traces of products were detected without using any base (Table 2, Entry 11).

We applied these optimized conditions to other substrates, and the results are summarized in Table 3.[11] It was found that the reaction works well with different substituents. Various R groups at the β'-position, such as vinyl (Entries 1 and 8), alkyl (Entries 2 and 4), and phenyl (Entry 3), gave high stereoselective with



Scheme 3. Plausible reaction mechanism for dehydrogenation process.

moderate yield. Other substituted group such as benzoyl and ester group were also combined into products (Entries 5 and 6). Whereas the substrate with two substituents at β-position failed (Entry 10). In general, the R group in product **2** was arrayed on the (*Z*)-position to more bulky carbonyl group,[12] which is different from the product which was obtained by the Knoevenagel condensation.

In other hypervalent aryl-λ^3-iodanes-mediated oxidation procedures, the heteroatom ligands on iodine(III) serve as leaving groups in both the ligand-exchange step and the reductive elimination process of λ^3-iodanyl groups.[1–5] Following these general considerations, one plausible reaction mechanism was proposed and outlined in Scheme 3.

In conclusion, a new synthetic reaction of α-ylidene-β-dicarbonyl compounds with high stereoselectivity from corresponding α-alkyl-β-dicarbonyl ones has been developed by using low toxic $PhI(OAc)_2$ under mild conditions, which could be complementary for the Knoevenagel condensation.

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11 General procedure for α-ylidene-β-dicarbonyl compounds: A typical procedure is given for the synthesis of **2a**. A mixture of α-alkyl-β-dicarbonyl **1a** (0.2023 g, 1 mmol), $PhI(OAc)_2$ (0.6442 g, 2 mmol), and $KHCO_3$ (0.2200 g, 2.2 mmol) was dissolved in MeCN (10 mL) at room temperature, and stirred at this temperature for 1 h. The TLC showed the reaction was completed. The solvent was removed in vacuo, and purified by chromatography (PE:EtOAc = 5/1) to give the title compound **2a** (0.1062 g, 53%). For details, refer to the Supporting Information which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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