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Base-Promoted Oxidative C−H Functionalization of α-Amino Carbonyl Compounds under Mild Metal-Free Conditions: Using Molecular Oxygen as the Oxidant

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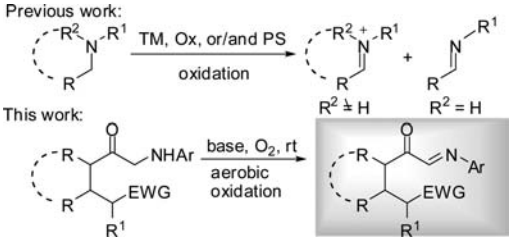
Supporting Information

ABSTRACT: A base-mediated aerobic oxidation of the C−H bond adjacent to the N-atom of a secondary amine to form an imine intermediate under mild metal-free basic conditions has been developed. Accordingly, this new strategy has been successfully applied to the synthesis of various di-, tri-, and tetra-substituted α-aminocyclopentenones through a tandem aerobic oxidative [4 + 1] carbocyclization reaction of *N*-aryl α′-amino-α,β-unsaturated ketones as C_4 1,4-dielectrophiles with active methylenes, including ethyl isocyanoacetate, nitroalkanes, and ethyl cyanoacetate, as C_1 components.

During the past decade, direct C−H functionalization reactions have been widely studied and realized to be important for constructing valuable compounds from simple precursors.[1] In this field, the cross-dehydrogenative coupling[2−5] (CDC) including cross-coupling hydrogen evolution (CCHE)[2g] reactions for C−C bond formations enables the direct construction of a new C−C bond under redox conditions. Such methods are highly sought after because these reactions do not require prefunctionalization of subcomponents and, as a result, have high atom economy. Yet, in the CDCs,[2−4] transition metal (TM) catalysts/mediators, chemical oxidants (Ox), and/or photosensitizers (PS, in light induced DCD) are generally required to afford an active electrophilic intermediate, such as an iminium ion or an imine from a tertiary and secondary amine,[3,4] respectively (Scheme 1, previous work).[5]

Scheme 1. Generation of Electrophiles in CDC



As valuable compounds, cyclopentenones have been found in various natural products and pharmaceuticals[6−11] and applied as useful building blocks in organic synthesis.[7−11] Methodologically, cyclopentenones are constructed mainly by Nazarov cyclization of divinyl ketones[7] or allene ethers[8] and by Piancatelli rearrangement of α-furylcarbinols[9] via a conrotatory 4π electrocyclization in the presence of Brønsted or Lewis acid catalysts,[7−9] or by the Pauson−Khand reaction, a dicobalt-octacarbonyl-mediated [2 + 2 + 1] carbocyclization for joining an alkene, an alkyne, and carbon monoxide.[10,11]

In our recent research, several novel tandem reactions based on α-acidic isocyanides[12] have been disclosed,[13,14] and ethyl isocyanoacetate has been used as a double Michael donor in Michael addition based domino reactions,[14] for example, the reactions with C_5 1,5-dielectrophiles[14a−c] or C_7 1,7-dielectrophiles.[14d] On the other hand, it was found that the C−H bond adjacent to the nitrogen in *N*-substituted tetramic acids as tertiary amines can be oxidized under ambient conditions in the presence of a base using O_2 (from air) as the oxidant.[15a] These results[14,15] combined with the development of CDC reactions[2,3] including cross-dehydrogenative Mannich-type reactions of α-amino carbonyl derivatives in the presence of transition metal catalysts/mediators, oxidants, or photosensitizers (Scheme 1, previous work)[2b,4] prompted us to investigate the CDC reactions of ethyl isocyanoacetate with *N*-aryl α′-amino-α,β-unsaturated ketones as C_4 1,4-dielectrophiles under basic conditions using O_2 as the oxidant in the absence of transition metal catalysts/promoters, chemical oxidants, and photosensitizers. This investigation has led us to develop a simple and efficient approach to the synthesis of highly substituted cyclopentenones from reactions of readily available *N*-aryl α′-amino-α,β-unsaturated ketones as C_4 1,4-dielectrophiles with activated methylene compounds, including ethyl isocyanoacetate, nitro alkanes, and ethyl cyanoacetate, respectively, as C_1 dinucleophiles, under very mild basic conditions using O_2 (from air) as the oxidant. Mechanistic studies reveal the in situ generation of imines from α-amino carbonyl compounds as secondary amines in the presence of a base under mild metal-free conditions (Scheme 1, this work). Herein, the formation of an imine intermediate by base-mediated aerobic oxidation of the C_{sp^3}−H

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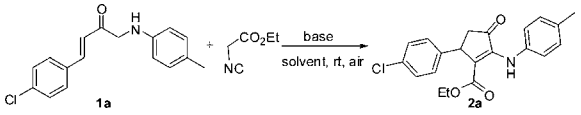
bond adjacent to the N-atom of a secondary amine, the synthetic application for the synthesis of cyclopentenones, and mechanistic studies are described.

The substrates, *N*-aryl α'-amino-α,β-unsaturated ketones **1**, were prepared by means of α-iodination of α,β-unsaturated methyl ketones[16] followed by amination of the resulting iodides.[17] After careful screening of reaction conditions, the reaction of α-amino carbonyl compound **1a** with ethyl isocyanoacetate gave 5-(4-chlorophenyl)-3-oxo-2-(*p*-tolylamino)cyclopent-1-enecarboxylate **2a** in 87% yield via an oxidative [4 + 1] carbocyclization in the presence of Cs_2CO_3 (0.7 equiv) in DMF at rt in open air for 1 h (entry 1).[18] Interestingly, either decreasing or increasing the amount of Cs_2CO_3 led to lower yields of **2a** (entries 2 and 3). In comparison, other bases such as DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene), NaOH, *t*-BuOK, Et_3N, and DABCO (1,4-diazabicyclo[2.2.2]octane) were less (Table 1, entries 4, 7, and 8) or not effective (entries 5 and 6). The solvent, DMF, was optimal (entry 1) compared to other solvents examined, including THF, CH_3CN, $Cl(CH_2)_2Cl$ (DCE), and EtOH (entries 9–12).

Table 1. Optimization of Reaction Conditions



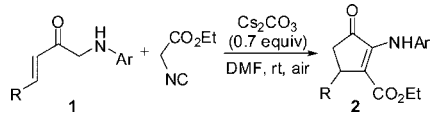
entry	base (equiv)	solvent	time (h)	yield (%)[a]
1	Cs_2CO_3 (0.7)	DMF	1	87
2	Cs_2CO_3 (0.5)	DMF	2	72
3	Cs_2CO_3 (1.0)	DMF	1	81
4	DBU (0.7)	DMF	1	47
5	DABCO (0.7)	DMF	3	–
6	Et_3N (0.7)	DMF	3	–
7	NaOH (0.7)	DMF	6	32
8	*t*-BuOK (0.7)	DMF	1	75
9	Cs_2CO_3 (0.7)	MeCN	1	67
10	Cs_2CO_3 (0.7)	THF	8	17
11	Cs_2CO_3 (0.7)	DCE	1	76
12	Cs_2CO_3 (0.7)	EtOH	1	78

[a]Isolated yields.

Under the optimal conditions, the scope of the oxidative [4 + 1] carbocyclization for the preparation of 2-amino-3-ethoxycarbonyl cyclopentenones **2** with ethyl isocyanoacetate as the C_1 component was investigated, and the results are summarized in Table 2. All of the selected substrates **1a–h**, bearing phenyl (entry 4), electron-deficient (entries 1–3) and electron-rich aryl (entries 5 and 6), heteroaryl (entry 7), and 1-naphthyl (entry 8) groups at the β-position of the enone moiety, reacted smoothly with ethyl isocyanoacetate to give the desired cyclopentenones **2a–h** in high to excellent yields at rt in open air for 0.8–4 h. Also, the reaction of substrate **1i** bearing an (*E*)-phenylvinyl group (R) gave the desired product **2i** in 62% yield (entry 9). Yet, various *N*-aryl groups of **1** were also well-tolerated and the corresponding cyclopent-2-enones **2j–l** were prepared in good to high yields (entries 10–12).

Several typical reactions were performed to understand the reaction in detail. Under identical conditions as mentioned above, the reaction of 1-cyclohexenyl-2-(*p*-tolylamino)ethanone **1m** with ethyl isocyanoacetate gave the desired bicyclic product **2m** in 56% yield (Scheme 2, eq 1), indicating the wide scope of the [4 + 1] carbocyclization. When the reaction of **1a** with ethyl isocyanoacetate was carried out under a nitrogen atmosphere, the Michael adduct **3a** was obtained in 85% yield (Scheme 2, eq 2). Treatment of **3a** with Cs_2CO_3 in open air led to cyclopentenone **2a** in 92% yield (Scheme 2, eq 2). Also, under essentially identical conditions as mentioned above (Table 1, entry 1), the [4 + 1] carbocyclization reaction of imine **4a** with ethyl isocyanoacetate can smoothly proceed to give the desired product **2a** in 89% yield (Scheme 2, eq 3), whereas **2a** was produced in only 23% yield in the presence of *tert*-butylmercaptan (1.2 equiv) as a radical inhibitor (Scheme 2, eq 4). These results indicate that O_2 as the oxidant (from air) is necessary for the oxidative [4 + 1] carbocyclization reaction of **1** or **3a** and a radical mechanism may be involved in this oxidative cyclization process.

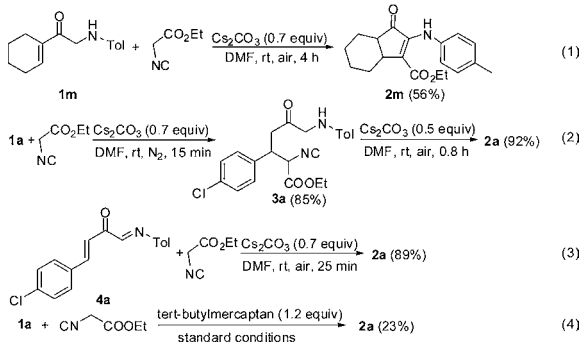
Table 2. Synthesis of 2-Amino-3-ethoxycarbonyl Cyclopentenones 2[a]



entry	1	R	Ar	time (h)	2	yield (%)[b]
1	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	1	**2a**	87
2	**1b**	2-ClC_6H_4	4-$CH_3C_6H_4$	0.8	**2b**	90
3	**1c**	4-$F_3CC_6H_4$	4-$CH_3C_6H_4$	1	**2c**	86
4	**1d**	C_6H_5	4-$CH_3C_6H_4$	3	**2d**	83
5	**1e**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3	**2e**	91
6	**1f**	3,4-$O_2CH_2C_6H_3$	4-$CH_3C_6H_4$	3	**2f**	77
7	**1g**	2-Thienyl	4-$CH_3C_6H_4$	3	**2g**	92
8	**1h**	1-Naphthyl	4-$CH_3C_6H_4$	2	**2h**	90
9	**1i**	$C_6H_5CH{=}CH$	4-$CH_3C_6H_4$	3	**2i**	62
10	**1j**	4-ClC_6H_4	4-ClC_6H_4	4	**2j**	60
11	**1k**	4-ClC_6H_4	C_6H_5	4	**2k**	63
12	**1l**	4-ClC_6H_4	3-$CH_3C_6H_4$	4	**2l**	82

[a]Reaction conditions: **1** (0.2 mmol), ethyl isocyanoacetate (0.24 mmol), Cs_2CO_3 (0.14 mmol), DMF (2.0 mL), rt in open air. [b]Isolated yields.

Scheme 2. Typical Reactions



The above oxidative [4 + 1] carbocyclization reaction provides an efficient access to 3-ethoxycarbonyl cyclopentenones **2** under very mild basic reaction conditions using O_2 as the oxidant (Table 2 and Scheme 2). This method hopefully constitutes an alternative to previously known approaches, such as Nazarov cyclization,[6,7] Piancatelli rearrangement,[8] and Pauson–Khand reaction.[9,10] Next, to broaden the scope of this valuable strategy, the aerobic oxidative [4 + 1] carbocyclization of selected *N*-aryl α'-amino-α,β-unsaturated ketones **1** with nitroalkanes **5** as the

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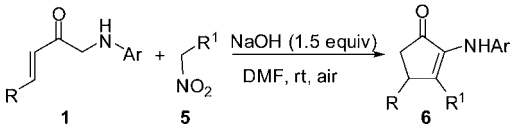
C_1 component was examined.[19] It was found that NaOH was a suitable base in DMF for the oxidative [4 + 1] carbocyclization (Table 3) and *N*-aryl 2-amino-cyclopentenones **6** were prepared

Table 3. Synthesis of *N*-Aryl 2-Amino-cyclopentenones 6[a]



1 5 6

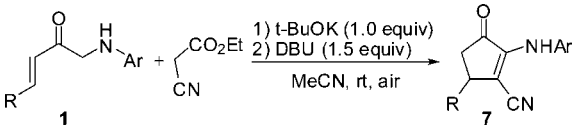
entry	1	R	Ar	R^1	time (h)	6	yield (%)[b]
1	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	Me	3	**6a**	80
2	**1d**	C_6H_5	4-$CH_3C_6H_4$	Me	4	**6d**	81
3	**1e**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	Me	4	**6e**	79
4	**1f**	3,4-$O_2CH_2C_6H_3$	4-$CH_3C_6H_4$	Me	4	**6f**	86
5	**1g**	2-Thienyl	4-$CH_3C_6H_4$	Me	3	**6g**	79
6	**1h**	1-Naphth	4-$CH_3C_6H_4$	Me	3	**6h**	81
7	**1k**	4-ClC_6H_4	C_6H_5	Me	3	**6k**	75
8	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	Et	3	**6l**	82
9	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	H	1.5	**6m**	45
10	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	CO_2Et	10	**2a**	73[c]

[a]Reaction conditions: **1** (0.2 mmol), nitroalkanes **5** (0.3 mmol), NaOH (0.3 mmol), DMF (2.0 mL), rt in open air. [b]Isolated yields. [c]DBU was used as base.

in good to high yields where the R^1 group is Me (**5a**, entries 1−7), Et (**5b**, entry 8), and H (**5c**, entry 9), respectively. For the case of the reaction of **1a** with ethyl nitroacetate **5d**, 3-ethoxycarbonyl cyclopentenone **2a** was obtained in 70% yield with elimination of the nitro group (entry 10).[19]

Furthermore, the reactions of selected *N*-aryl *α*′-amino-*α*,*β*-unsaturated ketones **1** with ethyl cyanoacetate as the C_1 component were also studied. Yet, under the identical conditions for the synthesis of 3-ethoxycarbonyl cyclopentenones **2** (Table 2), the reaction of **1a** with ethyl cyanoacetate was very sluggish. After further optimization of reaction conditions, fortunately, the oxidative [4 + 1] carbocyclization product, 5-(4-chlorophenyl)-3-oxo-2-(*p*-tolylamino)cyclopent-1-enecarbonitrile **7a**, was produced in 70% yield from the reaction of **1a** with ethyl cyanoacetate in acetonitrile in the presence of *t*-BuOK (1.0 equiv) and DBU (1.5 equiv) as bases at rt in open air (Table 4). Similarly, the corresponding 2-amino-3-cyano cyclopentenones **7b**, **7d**−**g**, and **7k** were prepared in good to high yields from reactions of ethyl cyanoacetate with **1b**, **1d**−**g**, and **1l**, respectively (Table 4, entries 2−7).

Table 4. Synthesis of 2-Amino-3-cyano Cyclopentenones 7[a]



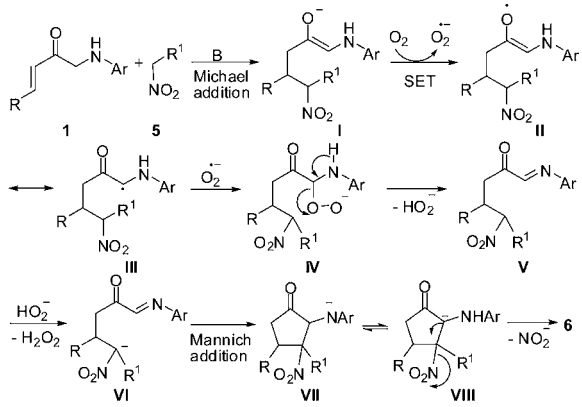
1 7

entry	1	R	Ar	time (min)	7	yield (%)[b]
1	**1a**	4-ClC_6H_4	4-$CH_3C_6H_4$	55	**7a**	70
2	**1b**	2-ClC_6H_4	4-$CH_3C_6H_4$	35	**7b**	58
3	**1d**	C_6H_5	4-$CH_3C_6H_4$	50	**7d**	61
4	**1e**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	35	**7e**	68
5	**1f**	3,4-$O_2CH_2C_6H_3$	4-$CH_3C_6H_4$	45	**7f**	55
6	**1g**	2-Thienyl	4-$CH_3C_6H_4$	50	**7g**	71
7	**1k**	4-ClC_6H_4	C_6H_5	40	**7k**	46

[a]Reaction conditions: **1** (0.2 mmol), ethyl cyanoacetate (0.24 mmol), *t*-BuOK (0.2 mmol), DBU (0.3 mmol), MeCN (2.0 mL), rt in open air. [b]Isolated yields.

Based on the above-mentioned experimental results and related reports,[2−5,19,20] a mechanism for the formation of 2-amino-cyclopentenones **6** is proposed (Scheme 3). This

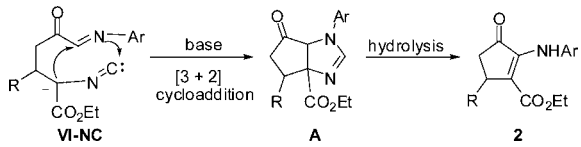
Scheme 3. Proposed Mechanism for Formation of 6



mechanism involves (1) Michael addition of nitroalkane **5** to *N*-aryl *α*′-amino-*α*,*β*-unsaturated ketones **1** under basic conditions to give Michael adduct **3** (Scheme 2, eq 2)[19] and further to form enolate intermediate **I**; (2) oxidation of **I** by O_2 via a single-electron transfer (SET) process to deliver a superoxide anion radical and the radical intermediate **II** in resonance with **III** followed by the reaction of **III** with the superoxide anion radical to generate anion intermediate **IV** having the hemiaminal-like structure;[2f,5,20] (3) as the crucial transformation, elimination of hydroperoxide anion from **IV** leading to imine intermediate **V**; and (4) deprotonation of *α*-acidic CH of **V** and subsequent intramolecular Mannich addition reaction giving amide intermediate **VII** and then carboanion intermediate **VIII**, where elimination of the nitro group[19] completes the oxidative [4 + 1] carbocyclization to give 2-amino-cyclopentenones **6**.

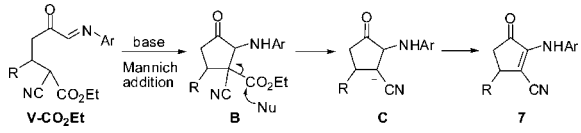
For the formation of 2-amino-3-ethoxycarbonyl cyclopentenones **2** with ethyl isocyanoacetate as the C_1 component (Table 2), the stepwise intramolecular [3 + 2] cycloaddition of intermediate **VI-NC** leads to the imidazoline intermediate **A**.[12] Hydrolysis of **A** affords 3-ethoxycarbonyl cyclopentenones **2** (Scheme 4).[21] In the hydrolysis process, the counterion of the base seems to play an important role (Table 1).

Scheme 4. Proposed Mechanism for Formation of 2



However, the mechanism for the formation of oxidative [4 + 1] carbocyclization products **7** could not be the same as described in Scheme 3 because ethoxycarbonyl is not a good leaving group. A driving force as described in Scheme 5, thereby,

Scheme 5. Proposed Mechanism for Formation of 7



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assisting ethoxycarbonyl "elimination" should be involved. Thus, the formation of **7** may proceed via base-mediated intramolecular Mannich addition reaction to give cyclopentanone intermediate **B** followed by the DBU-assisted cleavage of the ethoxycarbonyl group[22] from intermediate **B** and subsequent loss of proton to generate **7** (Scheme 5).

In conclusion, the base-mediated aerobic oxidation of the C−H bond adjacent to the nitrogen of *N*-aryl α'-amino-α,β-unsaturated ketones **1** to generate an imine intermediate under mild metal-free conditions has been developed. This new transformation enabled the synthesis of a wide variety of substituted cyclopentenones, such as tri- or tetra-substituted 2-amino-3-ethoxycarbonyl cyclopentenones **2**, 2-amino-cyclopentenones **6**, and 2-amino-3-nitrile cyclopentenones **7** through a base-mediated tandem process, involving Michael addition/aerobic oxidation/intermolecular Mannich-type addition/elimination, namely aerobic oxidative [4 + 1] carbocyclization, using readily available *N*-aryl α'-amino-α,β-unsaturated ketones **1** as C_4 1,4-dielectrophiles and active methylenes, including ethyl isocyanoacetate, nitroalkanes, and ethyl cyanoacetate as the C_1 components, respectively. All the reactions can proceed under very mild metal-free conditions using O_2 as the oxidant in a single operation to give the corresponding products in good to excellent yields. Efforts toward expanding the scope and utility of this new transformation from amines to imines are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of data for all new compounds, and X-ray crystallographic data (CIF) for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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