Copper-Catalyzed One-Pot Oxidation–Aldol/Henry Reaction of Benzylic Amines to α,β-Unsaturated Methyl Ketone/Nitro Compounds

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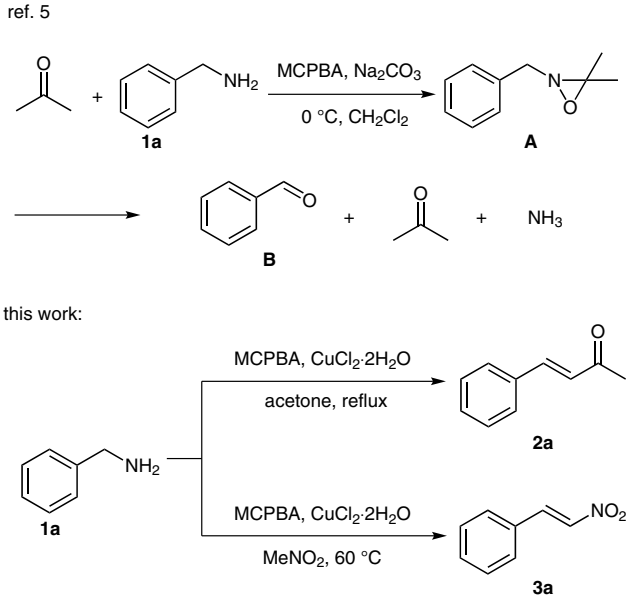
Abstract: A novel one-pot synthesis of α,β-unsaturated methyl ketone/nitro compounds from benzylic amines through an oxidation–aldol/Henry reaction is reported. The reaction proceeded well by using MCPBA as oxidant and $CuCl_2·2H_2O$ as catalyst. A variety of functionalized α,β-unsaturated methyl ketone/nitro compounds were assembled in moderate yields by application of this catalytic one-pot reaction.

Key words: aldol reaction, amines, copper, condensation, oxidation

α,β-Unsaturated methyl ketone/nitro compounds, which are not only present in many bioactive natural products[1] but also serve as useful electrophilic species in a broad range of chemical transformations such as Michael addition, cycloaddition and cross-coupling reactions,[2] have been drawing significant interest in the development of new methods in organic synthesis. Such compounds are generally obtained through aldol/Henry condensation of acetone/nitromethane with aldehydes.[3] A literature survey revealed that oxidation of amines to aldehydes had already been reported.[4] The wide availability of amines prompted us to consider such compounds as viable substrates for the oxidative preparation of the desired aldehydes. Moreover, a one-pot oxidation-aldol/Henry approach could eliminate the difficulties associated with aldehyde separation and purification. In 1971, Blackman[5] reported the oxidation of benzylamine (**1a**) to benzaldehyde by MCPBA through the acidic hydrolysis of an intermediate oxaziridine (Scheme 1). In this paper, the oxidation of benzylic amines and its condensation with acetone/nitromethane to form α,β-unsaturated methyl ketone/nitro compounds is reported (Scheme 1).

Initially, optimization of the reaction conditions was examined. The oxidation of **1a** in acetone with MCPBA (1.1 equiv) at 0 °C afforded oxaziridine as the major product (Table 1, entry 1). Reaction at room temperature provided a mixture of oxaziridine, benzaldehyde and (*E*)-4-phenylbut-3-en-2-one (**2a**; Table 1, entry 2). By increasing the temperature to reflux (60 °C), only **2a** could be isolated (49% yield; Table 1, entry 3). When the amount of MCPBA was increased to 1.5 equiv, benzaldehydeoxime **C** was the main product instead of the desired product **2a** (Table 1, entry 4).



Scheme 1 The oxidation of benzylamine by MCPBA

Lewis acids are well-known catalysts for the aldol reaction and they are often used because of their simple operation and low cost. Several enolate derivatives have been studied such as magnesium,[6] aluminum,[7] iron,[8] and zinc enolates.[9] On the basis of the previously developed reaction conditions, the influence of different Lewis acids was investigated. When $CuSO_4·5H_2O$, $ZnCl_2$, ZnI_2, $LiCl·H_2O$ and $LiBr·H_2O$ were used, the reactions tended to stop at the benzaldehyde stage (Table 2, entries 1–5). However, the reaction could be conducted with 10 mol% $FeCl_3$, $CuCl_2·2H_2O$, or $CuCl_2$ (Table 2, entries 6, 7 and 10), and $CuCl_2·2H_2O$ afforded the desired product **2a** with the highest yield (Table 2, entry 7). By adjusting the amount of $CuCl_2·2H_2O$, it was found that 25 mol% $CuCl_2·2H_2O$ was optimal (Table 2, entries 7–9 and 11).

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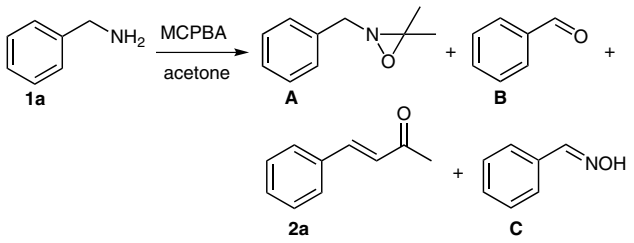
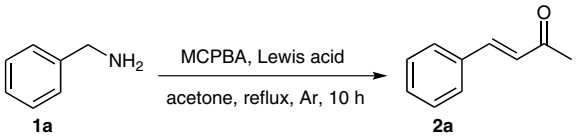
Table 1 Optimization of Reaction Conditions[a]



Entry	MCPBA (equiv)	Temp	A	B	2a	C
1	1.1	0 °C	*[b]	*[c]	*[c]	–
2	1.1	r.t.	*[b]	*[c]	*[c]	–
3	1.1	reflux	–	*[c]	49%[d]	–
4	1.5	reflux	–	*[c]	–	60%[d]

[a] Reaction conditions: benzylamine **1a** (5 mmol), acetone (25 mL), 10 h.
[b] The structure of this compound was determined by NMR spectroscopic analysis.
[c] This compound was detected by TLC analysis against a standard.
[d] Isolated yield.

Table 2 Lewis Acids in the Oxidation–Aldol Reaction[a]

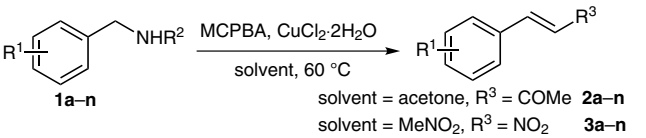


Entry	Lewis acid	Mol%	Yield (%)[b]
1	$CuSO_4·5H_2O$	10	trace
2	$ZnCl_2$	10	trace
3	ZnI_2	10	trace
4	$LiCl·H_2O$	10	trace
5	$LiBr·H_2O$	10	trace
6	$FeCl_3$	10	32
7	$CuCl_2·2H_2O$	10	60
8	$CuCl_2·2H_2O$	5	55
9	$CuCl_2·2H_2O$	25	65
10	$CuCl_2$	25	58
11	$CuCl_2·2H_2O$	50	33

[a] Reaction conditions: **1a** (5 mmol), MCPBA (5.5 mmol), acetone (12 mL), reflux, 10 h.
[b] Isolated yield.

We then examined the scope of the oxidation–aldol reaction. Various substituted benzylamines **1** were investigated under the optimized reaction conditions (Table 3). Substrates with both electron-donating groups and electron-withdrawing groups smoothly underwent the transformation, generating the desired products **2** in moderate yields. It can be seen that all the substituted benzylamines gave lower yields than benzylamine (**1a**). The reaction of secondary amine **1b** with MCPBA (2.1 equiv) and $CuCl_2·2H_2O$ (50 mol%) proceeded to give **2a** in 44% yield (Table 3, entry 2). The lower yield in the case of 2-chloro-3,6-difluorobenzylamine as substrate may be due to steric hindrance (Table 3, entry 12).

Table 3 Substrate Scope



Entry	R^1	R^2	**2** (%)[a,c]	**3** (%)[b,c]
1	H	H	65	61
2	H	Bn	44[d]	50[e]
3	4-OMe	H	50	45
4	4-F	H	61	48
5	3-F	H	44	41
6	$3\text{-}CF_3$	H	52	76
7	$2\text{-}CF_3$	H	47	60
8	3-Cl-4-Me	H	51	36
9	$3,4\text{-}Cl_2$	H	63	55
10	$2,5\text{-}F_2$	H	53	51
11	3-Me-4-F	H	45	31
12	$2\text{-Cl-}3,6\text{-}F_2$	H	37	trace
13	3-CN	H	34	–[f]
14	4-Cl	H	–[f]	62

[a] Reaction conditions (unless otherwise noted): **1** (5 mmol), MCPBA (5.5 mmol), 25 mol% $CuCl_2·2H_2O$, acetone (12 mL), reflux, 10 h.
[b] Reaction conditions (unless otherwise noted): **1** (5 mmol), MCPBA (5.5 mmol), 5 mol% $CuCl_2·2H_2O$, $MeNO_2$ (12 mL), 60 °C, 10 h.
[c] Isolated yield.
[d] Reaction conditions: **1a** (5 mmol), MCPBA (11 mmol), 50 mol% $CuCl_2·2H_2O$, acetone (20 mL), reflux, 10 h.
[e] Reaction conditions: **1a** (5 mmol), MCPBA (11 mmol), 10 mol% $CuCl_2·2H_2O$, $MeNO_2$ (20 mL), 60 °C, 10 h.
[f] Not attempted.

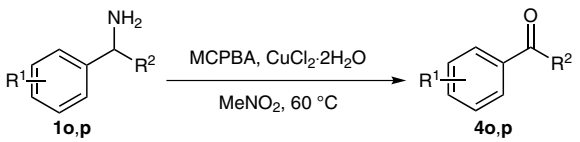
When nitromethane was used as solvent instead of acetone, we were pleased to find that the desired product (*E*)-2-nitro-1-phenylethene (**3a**) was generated in 58% yield. Further screening of the amount of $CuCl_2·2H_2O$ required for this reaction showed that 5 mol% $CuCl_2·2H_2O$ was sufficient.

To further establish the scope of the reaction, the optimized conditions were applied to various substituted benzylamines and the results are summarized in Table 3. Transformations of benzylamine derivatives containing either electron-donating or electron-withdrawing substit-

uents at different positions, proceeded efficiently to give the corresponding nitroalkene derivatives in moderate yields. It was confirmed that the steric hindrance of substrates had a limited effect on the yields of the reactions (Table 3, entries 4–7 and 12).

With the reaction conditions described above, the scope of this oxidation system was studied further with α-substituted benzylamines. Unfortunately, under neither conditions did 4-chloro-α-methylbenzylamine (**1o**) produce the corresponding α,β-unsaturated methyl ketone/nitro compound. Instead, when **1o** was treated with MCPBA (1.1 equiv) and $CuCl_2·2H_2O$ (5 mol%) in nitromethane at 60 °C, it was found that 1-(4-chlorophenyl)ethanone (**4o**) was generated in 52% yield (Table 4, entry 1). Thus, by using this approach, the resultant carbonyl compounds could be obtained from α-substituted benzylamines in moderate yields (Table 4, entries 1 and 2).

Table 4 Substrate Scope and Limitations[a]



1o,p **4o,p**

Entry	R^1	R^2	Product	Yield (%)[b]
1	4-Cl	Me	**4o**	52
2	2-Cl	CO_2Me	**4p**	64

[a] Reaction conditions: α-methylbenzylamine **1** (5 mmol), MCPBA (5.5 mmol), 5 mol% $CuCl_2·2H_2O$, $MeNO_2$ (12 mL), 60 °C, 10 h.
[b] Isolated yield.

In summary, a one-pot protocol that provides α,β-unsaturated methyl ketone/nitro compounds from benzylic amines under mild conditions, requiring catalytic $CuCl_2·H_2O$ and MCPBA as oxidant, has been established.[10] The advantages and limitations of this catalytic system were demonstrated. The ready availability of MCPBA and comparatively mild aldol/Henry condensation conditions of this protocol should provide an alternative choice for the preparation of functionalized α,β-unsaturated methyl ketone/nitro compounds.

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(10) **Oxidation–Aldol Reaction (Table 2); General Procedure:** Under an argon atmosphere, to a solution of benzylamine (5 mmol) and $CuCl_2·2H_2O$ (0.21 g, 1.25 mmol) in acetone (12 mL), MCPBA (1.12 g, 5.5 mmol) was added portionwise at 0 °C. The reaction mixture was heated at reflux in an oil bath with thorough stirring for 10 h (reaction monitored by TLC analysis). Upon cooling, saturated aqueous $Na_2S_2O_3$ (10 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was treated with 10% aq NaOH (15 mL) followed by extraction with EtOAc (3 × 10 mL). The combined extracts were washed with H_2O (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography (hexane–EtOAc).
Oxidation–Henry Reaction (Table 3); General Procedure: Under an argon atmosphere, to a solution of benzylamine (5 mmol) and $CuCl_2·2H_2O$ (0.04 g, 0.25 mmol) in $MeNO_2$ (12 mL), MCPBA (1.12 g, 5.5 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at 60 °C in an oil bath for 10 h (reaction monitored by TLC analysis). Upon cooling, saturated aqueous $Na_2S_2O_3$ (10 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was treated with 10% aq NaOH (15 mL) followed by extraction with EtOAc (3 × 10 mL). The combined extracts were washed with H_2O (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography (hexane–EtOAc).

