

## The Reactions of the Ozonides with Secondary Amines: An Efficient and Novel Way to Prepare Tertiary Amine from Mono- and 1,1-Di-substituted Alkenes via Corresponding Ozonides

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**Abstract:** The ozonolysis of mono- and 1,1-di-substituted olefins followed by treatment with secondary amines in the presence of 4 Å molecular sieves to give the corresponding tertiary amine in high yields. This transformation involved four sequential reactions in the same flask.

Reactions of some tertiary amines, and hindered secondary amines with the ozonides of 1-hexene and styrene were examined by Razumovskii *et al.*<sup>1</sup> In nonpolar media, they concluded that the reactions followed second order kinetics and that the radicals of N-oxides were formed in the first step. In other words, the electron transfer process occurred between the amine and the ozonide. Recently, we found that a tertiary amine or pyridine is better for the workup of the ozonolytic reaction than methyl sulfide.<sup>2</sup> The ozonide ring proton abstraction followed by the peroxide bond breakage and ring fragmentation was proposed to be the reaction pathway. In other words, the reaction was proposed to proceed via the E1cb mechanism in the first step.<sup>3</sup> Two different groups have come to different conclusions and provoked us to reinvestigate the reaction between the ozonide and secondary amine. The mono- or 1,1-di-substituted ozonide was treated with secondary amine to give a tertiary amine instead of a carbonyl compound as the sole product. The rationale of the product formation provides clear evidence to support our proposed mechanism. The potential of this transformation in organic synthesis was also described.

Since the yield of the ozonide formations from terminal olefins is excellent<sup>4</sup>, the ozonides could be prepared in situ at -78 °C and used for the further transformation in the same flask. The mono-substituted ozonide **2a** derived from 3-phenyl-1-butene (**1a**) in CH<sub>2</sub>Cl<sub>2</sub> was treated with piperidine (2.1 mole eq.) in the presence of 4 Å molecular sieves at room temperature and then heated up to reflux for 10 hr to give the *N*-3-phenylpropylpiperidine (**6**) in 85% yield (Scheme 1 and entry 1, Table 1). Similar result was obtained in high yield when the secondary amine such as morpholine, pyrrolidine, *N*-methyl-*N*-benzylamine or *N,N*-diisopropylamine was used (entries 2–5). The plausible mechanism for the formation of the *N*-3-phenylpropylpiperidine (**6**) was proposed as shown in Figure 1. The first equivalent of the piperidine abstracted the ozonide ring proton from the less hindered side followed by ring fragmentation to give the piperidinium formate (**4a**) and hydrocinnamaldehyde (**3a**).<sup>3</sup> The hydrocinnamaldehyde was then reacted with piperidine in the presence of 4 Å molecular sieves to give the corresponding enamine (**5a**)<sup>5</sup>, which was subsequently reduced to the tertiary amine (**3**) by piperidinium

Scheme 1

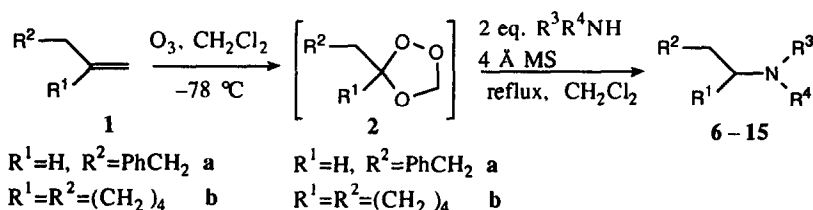


Table 1 : The formation of the Amines from Alkenes via One Pot Reaction

Entry	Starting Material	Product <sup>a</sup>	Yield (%)
1	$\text{R}^1=\text{H}, \text{R}^2=\text{PhCH}_2$ <b>1a</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2)_5-$	<b>6</b> 85
2	$\text{R}^1=\text{H}, \text{R}^2=\text{PhCH}_2$ <b>1a</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2)-$	<b>7</b> 72
3	$\text{R}^1=\text{H}, \text{R}^2=\text{PhCH}_2$ <b>1a</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2)_4-$	<b>8</b> 76
4	$\text{R}^1=\text{H}, \text{R}^2=\text{PhCH}_2$ <b>1a</b>	$\text{R}^3 = \text{Me}, \text{R}^4 = \text{CH}_2\text{Ph}$	<b>9</b> 81
5	$\text{R}^1=\text{H}, \text{R}^2=\text{PhCH}_2$ <b>1a</b>	$\text{R}^3 = \text{R}^4 = \text{CH}(\text{i-Pr})_2$	<b>10</b> 83
6	$\text{R}^1=\text{R}^2=(\text{CH}_2)_4$ <b>1b</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2)-$	<b>11</b> 87
7	$\text{R}^1=\text{R}^2=(\text{CH}_2)_4$ <b>1b</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2)_4-$	<b>12</b> 86
8	$\text{R}^1=\text{R}^2=(\text{CH}_2)_4$ <b>1b</b>	$\text{R}^3 = \text{Me}, \text{R}^4 = \text{CH}_2\text{Ph}$	<b>13</b> 79
9	$\text{R}^1=\text{R}^2=(\text{CH}_2)_4$ <b>1b</b>	$\text{R}^3 = \text{R}^4 = \text{CH}(\text{i-Pr})_2$	<b>14</b> 0 <sup>b</sup>
10	$\text{R}^1=\text{R}^2=(\text{CH}_2)_4$ <b>1b</b>	$\text{R}^3 = \text{R}^4 = -(\text{CH}_2)_5-$	<b>15</b> 0 <sup>c</sup>

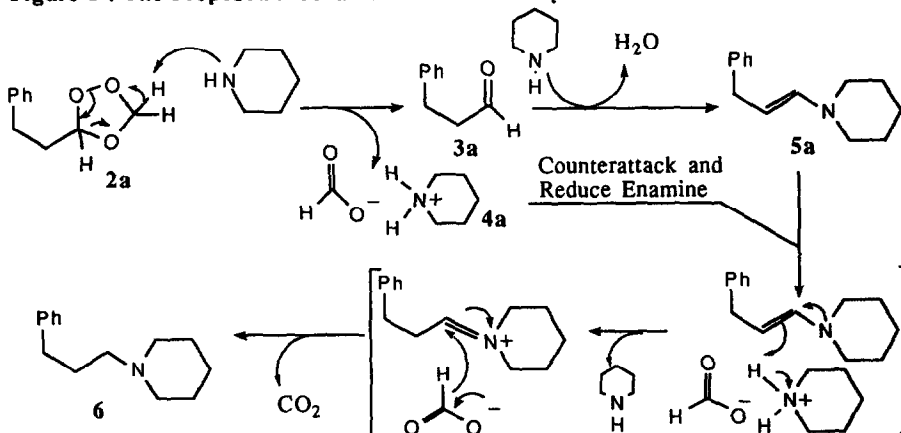
<sup>a</sup> All of the products were characterized by exact mass, IR, and (1H, 13C) NMR. <sup>b</sup> The cyclohexanone was obtained in 83% yield. <sup>c</sup> The 2-piperidin-1-ylmethyl-cyclohexanone (**16**) was obtained in 74% yield.

formate.<sup>8</sup> There are four sequential reactions occurred in the same flask starting from the alkene. The enamine was reduced by formic acid to the saturated amine is called the Wallach reaction in which the hydride transfer process was involved.<sup>6</sup> It is possible to use piperidinium formate as a substitute for the Wallach conditions.<sup>7</sup>

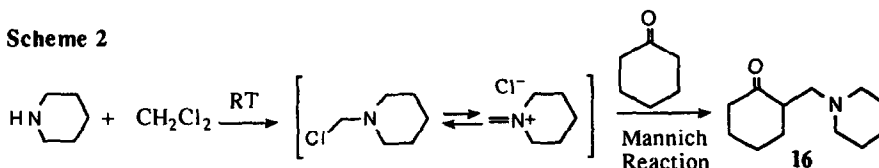
In order to understand whether the 1,1-disubstituted alkenes could also be carried out similar transformation, methylenecyclohexane (**1b**) was demonstrated. The yield of the ozonide formation from methylenecyclohexane is better in *n*-pentane than in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C.<sup>8,9</sup> After ozonolysis, *n*-pentane was removed by rotary evaporator at room temperature and changed to CH<sub>2</sub>Cl<sub>2</sub>. To the resulting solution was added the morpholine (2.1 mole eq.) and molecular sieves and then heated up to reflux for 10 hr. The *N*-cyclohexylmorpholine (**11**) was formed in good yield (entry 6). Similar results were obtained when pyrrolidine, or *N*-methyl-*N*-benzylamine was used (entries 7–8). Their reaction pathway should be

similar to the one shown in Figure 1. When *N,N*-diisopropylamine was used, the cyclohexanone instead of tertiary amine was formed as the product in 83% yield (entry 9). Presumably, the enamine formation from *N,N*-diisopropylamine and cyclohexanone is difficult due to the steric hindrance. Although the *N*-cyclohexylmorpholine (11) was formed in good yield when morpholine was used (entry 6), there is no *N*-cyclohexylpiperidine (15) formation when the piperidine was used (entry 10). To our surprise, the Mannich product was isolated in good yield with methylene chloride as a one carbon unit (Entry 10 and Scheme 2).<sup>10</sup> It is not clear why the morpholine and piperidine showed so much difference in the present reaction. The enamine formation from piperidine and cyclohexanone is probably not a facile process.

**Figure 1 : The Proposed Mechanism of the Tertiary Amine Formation**

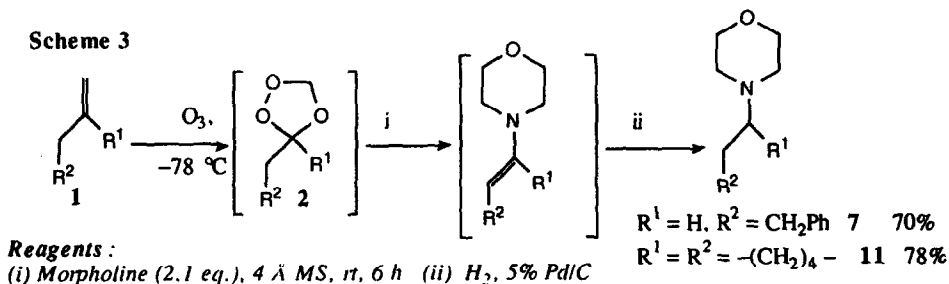


**Scheme 2**



The reaction temperature is important to the reductive amination. The reaction stopped at the enamine stage when the reaction is kept at room temperature. Obviously, the refluxing in  $\text{CH}_2\text{Cl}_2$  is needed to reduce the enamine by the ammonium formate. The enamine intermediates could also be reduced to

**Scheme 3**



tertiary amines (7 and 11) in high yield by catalytic hydrogenation (Scheme 2). It is also feasible to use these enamine intermediates for further functional group transformation<sup>5</sup> simply by controlling the reaction temperature.

We are pleased to discover the formation of ammonium formate by which our E<sub>1cb</sub> mechanism is fully supported (Fig.1). Neither the corresponding carbonyl compound nor its enamine was detected in the crude products indicated that the amount of the piperidinium formate is sufficient to reduce the enamine intermediate. Therefore, the deprotonation of the ozonide ring proton followed by ring fragmentation is the major pathway in the reaction of the ozonide and secondary amine.

In summary, the ozonides derived from the mono- and 1,1-di-substituted olefins react with secondary amines in the presence of 4 Å molecular sieves to give the corresponding tertiary amine in refluxing CH<sub>2</sub>Cl<sub>2</sub>. This transformation involved four sequential reactions in the same flask. When the reaction was kept at room temperature, the corresponding enamine was formed as the major product. We have demonstrated the versatile applications of the ozonide moiety in organic synthesis. Further synthetic applications of this transformation are under investigation.

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#### References and Notes:

- (a) Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*, Chapter 9, pp 370, Elsevier, Netherlands, 1984. (b) Pobedimskii, D.G.; Razumovskii, S.D. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 3, 602; *Chem. Abst.* **1970**, 73, 13853n.
- (a) Hon, Y.S.; Lin, S.W.; Chen, Y.J. *Synth. Commun.* **1993**, 23, in press. (b) Hon, Y.S.; Yan, J.L. *Tetrahedron Lett.* **1993**, 34, in press.
- Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry*, 3rd Ed., Chapter 6, Part A, Plenum Press, New York, N.Y., 1990.
- (a) Hon, Y.S.; Lu, L.; Chang, R.C.; Chu, K.P. *Heterocycles* **1991**, 32, 437. (b) Bailey, P.S. *Ozonation in Organic Chemistry*, Vol. 1, Academic Press, New York, 1978.
- (a) Cook, A.G. *Enamines: Synthesis, Structure, and Reactions*, Marcel Dekker, Inc., New York, New York, U.S.A., 1988. (b) Hickmott, P.W. *Tetrahedron* **1982**, 38, 1975. (c) Hickmott, P.W. *Tetrahedron* **1982**, 38, 3363.
- (a) Lukes, R.; Jizba, J. *Chem. Listy* **1953**, 47, 1336. (b) Leonard, N.J.; Sauers, R.R. *J. Am. Chem. Soc.* **1957**, 79, 6210.
- (a) Moore, M.L. *Org. React.* **1949**, 5, 301. (b) Noyce, D.S.; Bachelor, F.W. *J. Am. Chem. Soc.* **1952**, 74, 4577. (c) Lukasiewicz, A. *Tetrahedron* **1963**, 19, 1789. (d) Awachie, P.I.; Agwada, V.C. *Tetrahedron* **1990**, 46, 1899.
- Criegee, R.; Korber, H. *Adv. Chem. Ser.* **1972**, 112, 22.
- Besides the ozonide, cyclohexanone was also formed in 14% yield when methylenecyclohexane was ozonized in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. However, the formation of cyclohexanone was suppressed to minimum (8%) when the solvent was changed from CH<sub>2</sub>Cl<sub>2</sub> to *n*-pentane.
- (a) Matsumoto, K. *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 922. (b) Matsumoto, K.; Hashimoto, S.; Ikemi, Y.; Otani, S. *Heterocycles* **1984**, 22, 1417. (c) Souquet, F.; Martens, T.; Fleury, M-B. *Synth. Commun.* **1993**, 23, 817. (d) When the solvent was changed to benzene, neither reductive amination nor Mannich reaction occurred. The result indicates that the C-1 unit was indeed derived from CH<sub>2</sub>Cl<sub>2</sub>.

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