

Preparation of α -Substituted Acroleins via the Reaction of Aldehyde with Dihalomethane and Diethylamine

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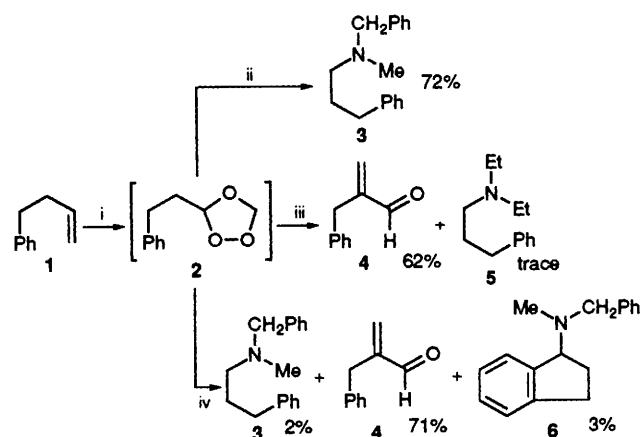
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Treatment of ozonides or aldehydes with a mixture of dihalomethane and diethylamine in dichloromethane affords α -substituted acroleins in good yields, the β -carbon of the acrolein being derived from dihalomethane; the relative rates and yields are in the following order: $\text{CH}_2\text{I}_2 > \text{CH}_2\text{Br}_2 > \text{CH}_2\text{Cl}_2$.

Ozonides derived from mono- and 1,1-di-substituted olefins react with secondary amines in refluxing CH_2Cl_2 in the presence of 4 Å molecular sieves to give the corresponding tertiary amines in good yields *e.g.* **2** to **3** (Scheme 1).¹ However, treatment of the ozonide with a secondary amine, diethylamine, afforded the α,β -unsaturated aldehyde **4** 62% yield with only a trace amount of the expected product **5**. Use of CH_2Br_2 as solvent gave the conjugated aldehyde **4** (70%), along with **3** (2%) and 1-aminointhane **6** (3%) resulting from the iminium ion cyclization. These results indicate that CH_2Cl_2 and CH_2Br_2 each provided one carbon unit in the major product. In the presence of a secondary amine, CH_2Cl_2 is known to behave both as solvent and reactant under high² or atmospheric pressure³ at room temperature. Methylene-bisamines were proposed as the intermediates. Mannich products have been obtained in modest to good yields by treating the proposed intermediate with ketone,^{2b} enamine,^{3d} or indole.^{2d} To the best of our knowledge, there is no literature precedent for our observed enal formation.⁴ In this report, we summarize the results of our work to investigate its scope.

As shown in Scheme 1, the reaction pathway is dependent on the structure of the secondary amine and dihalomethane. For example, Et_2NH reacts preferably with CH_2Cl_2 than with aldehyde because Et_2NH is a poor reagent for the enamine formation.⁵ However, enamine formation from *N*-methylbenzylamine and aldehyde is a facile process and reductive amination occurs to give **3** in CH_2Cl_2 , but in CH_2Br_2 *N*-methylbenzylamine prefers to react with the solvent rather than the aldehyde to give **4**.[†]

Table 1 lists the results of experiments to determine optimal conditions for the reaction.‡ Molecular sieves were not required for this reaction (entries 1 and 2) and 2.5 mol equiv. of diethylamine was sufficient to obtain the enal **4** in 61% yield. Extra diethylamine did not give an improvement in the chemical yield (entries 2, 3 and 4). Better chemical yields in a shorter reaction time were obtained when the solvent was changed from CH_2Cl_2 to CH_2Br_2 (entries 2 and 5). Mixed solvent systems also improved the yields (entries 2, 6 and 7).



Scheme 1 Reagents and conditions: i, O_3 , CH_2Cl_2 , -78°C ; ii, PhCH_2NHMe , heat, CH_2Cl_2 , 4 Å mol. sieves; iii, Et_2NH , heat, CH_2Cl_2 , 4 Å mol. sieves; iv, PhCH_2NHMe , heat, CH_2Br_2 , 4 Å mol. sieve

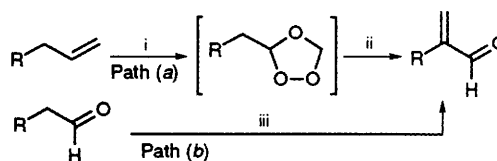
In order to alleviate the problem of product acid sensitivity, a mixture of diethylamine and CH_2Br_2 was preheated to 55°C for 1.5 h in an attempt to generate the reactive species in advance. To this mixture was then added a solution of the ozonide **2** in CH_2Cl_2 at room temperature. The reaction was found to be complete in 0.5 h and compound **4** was formed in 72% yield (entry 8). In light of its efficiency this procedure was used in further investigations.

We have previously reported that aldehydes are formed in good yield from the reaction of monosubstituted ozonides with tertiary or secondary amines.⁶ Therefore, 3-phenylpropionaldehyde should serve as an intermediate leading to 2-benzylacrolein **4** (Scheme 1). It is interesting to compare the results of α -substituted acrolein formation from olefin *via* ozonide [path (a)] and directly from the corresponding aldehyde [path (b)] under similar conditions (Scheme 2). The results listed in Table 2 indicate that the higher yields were obtained from path (b) (entries 1–5). The chemoselective formation of α -substituted acrolein in the presence of a ketone carbonyl is possible, and the protection of the keto group is actually not necessary (*cf.* entries 4 and 5). This method is also applicable to the preparation of oxygen- and nitrogen-substituted acroleins in modest yields (entries 3 and 6).

Table 1 2-Benzylacrolein **4** formation from the treatment of ozonide **2** (0.2 mol dm^{-3}) with dihalomethane and diethylamine

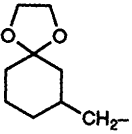
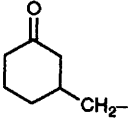
Entry	Et_2NH (equiv.)	Solvent	$T/^\circ\text{C}$	t/h	Yield (%)
1	2.5 ^a	CH_2Cl_2	Reflux	24	61
2	2.5	CH_2Cl_2	Reflux	24	61
3	4	CH_2Cl_2	Reflux	24	62
4	10	CH_2Cl_2	Reflux	24	62
5	2.5	CH_2Br_2	55	0.8	81
6	2.5	$\text{CH}_2\text{Br}_2/$ 10 equiv. ^c in CH_2Cl_2	55	16	71
7	2.5	$\text{CH}_2\text{I}_2/$ 6 equiv. in CH_2Cl_2	55	3	74
8	3 ^b	$\text{CH}_2\text{Br}_2/$ 10 equiv. in CH_2Cl_2	Room temp.	0.5	72

^a In the presence of 4 Å molecular sieves. ^b A solution of Et_2NH and CH_2Br_2 was heated at 55°C for 1.5 h prior to the addition of the ozonide in CH_2Cl_2 . ^c Relative to ozonide **2**.



Scheme 2 Reagents and conditions: i, O_3 , CH_2Cl_2 , -78°C ; ii, preheated mixture (55°C ; 1.5 h) CH_2Br_2 – Et_2NH (5 : 1); iii, preheated mixture (55°C ; 1.5 h) CH_2Br_2 – Et_2NH (3 : 1)

Table 2 α -Substituted acrolein formation from olefin *via* ozonide [path (a)] or from aldehyde [path (b)]

Entry	Starting material R =	t/h	Yield (%)	
			Path (a) ^b	Path (b)
1	PhCH ₂ -	0.5	72	87
2	Me(CH ₂) ₆ -	0.5	62	72
3	PhCH ₂ O-	0.5	61	73
4		0.5	67	72
5		0.5	63	73
6	PhCONH-	0.5 ^a	42	—

^a The reaction was carried out at -78 °C in CH₂Cl₂. ^b All of the products were characterized by exact mass, IR, and ¹H, ¹³C NMR.

Treatment of ketone with dihalomethane in the presence of secondary amine was shown to give the corresponding Mannich base.^{2b} Accordingly, Mannich base should be also formed first in our reaction, and the deamination of β -aminoaldehydes to give α -substituted acroleins must be a facile process under our reaction conditions. However, the detailed information about deamination remains to be studied.

In summary, the reactive intermediate generated from diethylamine and dibromomethane is an effective ingredient to convert the monosubstituted ozonides or aldehydes to the α -substituted acroleins. The reported procedure is a general and economic method to prepare α -alkyl-, α -alkoxy-, and α -amido-acroleins in good yields. The newly developed reaction conditions represent an excellent example of using dihalomethane as reactant in organic synthesis. Further synthetic applications and mechanistic aspects of the transformation are under current investigation.

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Footnotes

† The characteristic signals of the ¹H NMR spectrum of **4** are two singlets (δ 6.06 and 6.09) due to the olefinic protons. The assignment of the signal at δ 6.06 to the proton *cis* to the carbaldehyde group was confirmed by 2D-NOESY NMR technique.

‡ Standard procedure for 4-phenylbut-1-ene **1**. Ozone was bubbled through a solution of **1** in CH₂Cl₂ at -78 °C until the blue colour persisted. The excess of ozone was excluded by nitrogen stream. To the resulting solution was added diethylamine at room temperature and the reaction mixture was heated then concentrated to give a yellow solid which was washed with Et₂O, to remove the ammonium salt, concentrated and chromatographed on silica gel to give the desired 2-benzylacrolein **4**.

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