Addition of *N*-(Hydroxymethyl)phthalimide to Methacrylates by Carbon-Carbon Bond Formation

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Synopsis. *N*-(Hydroxymethyl)phthalimide undergoes addition to the carbon-carbon bond of methacrylates effectively in sulfuric acid, resulting in the formation of a new carbon-carbon bond.

The hydroxymethyl group attached to the nitrogen of imides exhibits an interesting reactivity owing to a distinct cationic nature of the methylene group in an acidic medium such as sulfuric acid. Compounds having such a group are thus interesting intermediates in organic synthesis as electrophiles. *N*-(Hydroxymethyl)phthalimide is, for example, capable of electrophilic addition to cyano groups to form amide-imide compounds.[1] It also undergoes dehydration reaction with amines, while affording amine-imide derivatives.[2] These characteristic reactions have proved useful in providing convenient methods for synthesizing various types of polyamide-imides[3] and polyamine-imides.[4] This peculiar electrophilicity of hydroxymethylimides suggests the possibility of additions to carbon-carbon double bonds, if adequately polarized to permit the electrophilic attack, leading to new addition products by carbon-carbon bond formation.

N-(Hydroxymethyl)phthalimide (**1**) was subjected to the reactions with various kinds of compounds having a carbon-carbon double bond in concentrated sulfuric acid at 18 °C. The reaction with methyl methacrylate (**2a**) resulted in the formation of two products. Structural analysis revealed the major product to be a 1 : 1 adduct **3a** (78.5% yield) formed as a result of the electrophilic attack of **1** to the β-position of **2a**.

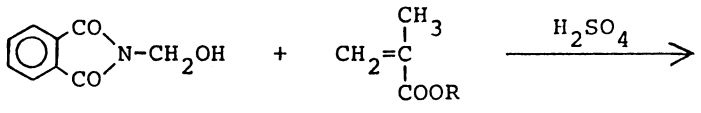
The minor product, on the other hand, was characterized by the presence of a carbon-carbon double bond and no hydroxyl group. Moreover, the ^{1}H NMR spectrum unambiguously indicated the double bond to be an exo methylene type. All these data supported the structure of **4a** (3.4% yield), which is formally a dehydrated form of **3a**. However, **3a** was not converted to **4a** when treated with sulfuric acid under the same conditions, suggesting **4a** to be formed by deprotonation from the intermediate species which results from the cationic attack of **1**, not by dehydration of **3a**. There is another possibility of deprotonation to give an alternate product having an endo double bond; however, **4a** was the only by-product we could isolate.

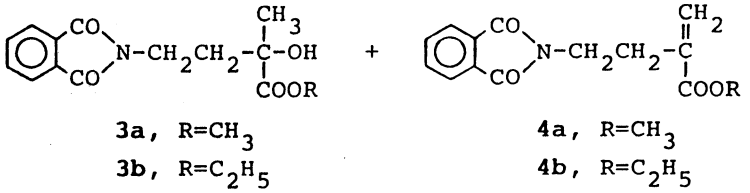
Since **1** seems to undergo decomposition in concentrated sulfuric acid in various fashions, the addition reaction would probably be dependent on the reaction temperature. When the temperature was lowered to 5 °C, the yield of **3a** increased to 82.0% as a result of suppression of side reactions at lower temperatures. Higher temperatures caused a marked reduction in the yield as shown in Table 1. In contrast, the formation of **4a** was not appreciably influenced by the reaction temperature. The reactions were also attempted in organic acidic solvents to prevent the possible degradation of **1** in sulfuric acid. No addition was, however, observed and only the starting materials were recovered in formic and dichloroacetic acids.

Ethyl methacrylate (**2b**) behaved quite similarly to **2a** in the reaction with **1** in sulfuric acid, giving the same kinds of addition products, **3b** and **4b**, in similar yields. Again, the minor product, **4b**, has an exo double bond.

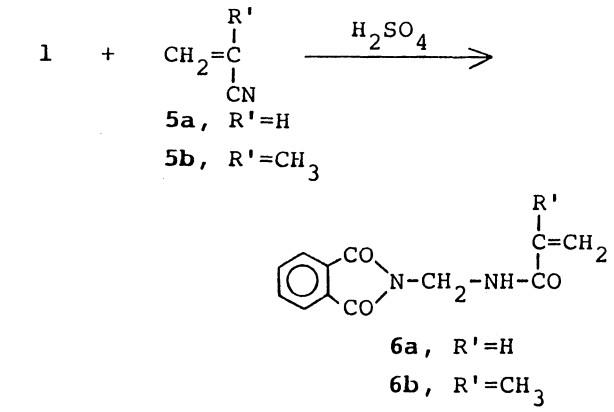
Table 1. Reaction of *N*-(Hydroxymethyl)-phthalimide **1** with Methacrylates **2**

Methacrylate	Condition		Yield	
	Temp/°C	Time/h	%	
2a	5	20	**3a**, 82.0	**4a**, 3.2
2a	5	40	**3a**, 80.0	**4a**, 3.0
2a	18	20	**3a**, 78.6	**4a**, 3.4
2a	30	20	**3a**, 60.0	**4a**, 2.5
2a	43	20	**3a**, 23.6	**4a**, 2.5
2b	18	20	**3b**, 82.0	**4b**, 5.0





If the addition of **1** also takes place to the carbon-carbon double bond as well as to the cyano group of acrylonitrile (**5a**) and methacrylonitrile (**5b**), these nitriles will afford 2 : 1 adducts. The addition reaction, however, turned out to proceed only at the cyano group even with two-fold excess **1**, and 1 : 1 adducts, **6a** and **6b**, were obtained in high yields along with three kinds of by-products formed from excess **1** by the elimination of formaldehyde and intermolecular dehydration. This indicates that the cyano group is more susceptible to electrophilic attack than the vinyl or vinylidene group on account of high electron density at the nitrogen atom and also that the resulting acrylamide and methacrylamide derivatives are resistive to the addition reaction.



Other vinyl compounds including methyl acrylate (**7**), ethyl acrylate (**8**), acrylic acid (**9**), methacrylic acid (**10**), methyl vinyl ketone (**11**), methyl isopropenyl ketone (**12**), acrylamide (**13**), vinyl acetate (**14**), butyl vinyl ether (**15**), styrene (**16**), fumaric acid (**17**), and cyclohexene (**18**) were also subjected to the reaction to understand the general scope of the reaction. No addition products were, however, detected in the reaction mixtures in all the cases, and only the by-products from **1** were isolated by column chromatography. It is noteworthy that while methacrylates **2a** and **2b** gave adducts in high yields, structurally similar vinyl compounds such as acrylates (**7** and **8**) and vinyl ketones (**11** and **12**) afforded no addition products, and only **1** and its degradation products were recovered. In the reaction with **11**, for example, most of the starting **1** was converted to the three kinds of by-products which were obtained in a total yield of 71%. This is probably ascribable to the higher electron availability at the α-position than β-position, as opposed to methacrylates,[8] which would make the reaction reluctant because of steric hindrance. Some reaction mixtures assumed dark colors and only small amounts of the by-products were recovered, indicating considerable extents of decomposition. The feasibility of the addition reaction thus appeared to be interpreted in terms of the electron availability at the β-position and the stability of the adducts; it is interesting to note that only the methacrylates meet these requirements among the vinyl compounds we examined.

Consequently, a new type of cationic addition of the hydroxymethyl group to C-C double bonds was effected, being quite sensitive to the substituents on the double bonds, and methacrylates were quite suitable for achieving a highly selective reaction.

Experimental

N-(Hydroxymethyl)phthalimide was prepared from phthalimide and formalin according to the procedure reported by Buc.[1]

^{1}H NMR spectra were recorded on a JEOL JNM-PMX60 (60 MHz) or JEOL JNM-GX270 (270 MHz) spectrometer, and ^{13}C NMR spectra on a JEOL PFT100 (25 MHz) or JEOL JNM-GX270 (68 MHz) spectrometer. Chemical shifts are relative to tetramethylsilane. IR spectra were taken with a JASCO IRA-1 spectrophotometer. Mass spectra were obtained with a Finnigan-MAT 4530 GC/MS spectrometer. Melting points were uncorrected.

Reaction of *N*-(Hydroxymethyl)phthalimide (1) with Methyl Methacrylate (2a). To 30 cm^3 of concentrated sulfuric acid kept at 0 °C was added 3.19 g (18 mmol) of pulverized **1**, which went into solution in 20 min with stirring. **2a** (1.80 g, 18 mmol) was added at 0 °C, and the solution was stirred at 18°C for 20 h. It was poured into ice-water, and the mixture was extracted with chloroform. The extract was washed with aqueous sodium hydrogencarbonate and then with water to neutral, dried over sodium sulfate, and evaporated to give 4.14 g of a white solid (mp 95—97 °C), whose TLC showed two spots. From the faster-moving band in column chromatography of the crude product on silicic acid in chloroform, an oily product was obtained and crystallized from acetone/petroleum ether to give 0.16 g (3.4% yield) of **4a** as colorless granules: mp 84—86 °C; IR (KBr) 1770, 1720 (shoulder), and 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.72 (t, 2H, J=6 Hz, CH_2), 3.78 (s, 3H, OCH_3), 3.91 (t, 2H, J=6 Hz, CH_2), 5.53 (d, 1 H, J=1 Hz, =CH_2), 6.15 (d, 1H, J=1 Hz, =CH_2), and 7.76 (m, 4H, Ar H). Found: C, 64.67; H, 4.96; N, 5.38%. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40%.

The slower-moving band gave 3.92 g of adduct **3a** (78.6% yield): mp 102—104 °C. Recrystallization from cyclohexane afforded colorless needles: mp 105—106 °C; IR (KBr) 3470 (OH), 1770, 1730 (shoulder), and 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.47 (s, 3H, CH_3), 2.13 (m, 2H, CH_2), 3.48 (br s, 1H, OH, exchangeable with D_2O), 3.69 (s, 3H, OCH_3), 3.80 (t, 2H, J=7 Hz, CH_2), and 7.78 (m, 4H, Ar H); ^{13}C NMR (DMSO-d_6) δ=25.97 (q, CH_3), 33.25 (t, CH_2), 37.67 (t, CH_2), 51.91 (q, OCH_3), 72.76 (s, -C-), 122.86 (d, Ar C), 131.74 (s, Ar C), 134.23 (d, Ar C), 167.61 (s, imide C=O), and 175.66 (s, C=O); MS m/z 277 (M^+). Found: C, 60.95; H, 5.37; N, 5.26%. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05%.

Reaction of *N*-(Hydroxymethyl)phthalimide (1) with Ethyl Methacrylate (2b). The reaction was carried out in the same way at 18°C for 20 h, and on chromatography, two products were isolated. One from the faster-moving band was an oil (adduct **4b**) which did not solidify (5.0% yield): IR (neat) 1770, 1730 (shoulder), and 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.31 (t, 3H, J=7 Hz, CH_3), 2.70 (t, 2H, J=7 Hz, CH_2), 3.88 (t, 2H, J=7 Hz, CH_2), 4.22 (q, 2H, J=7 Hz, OCH_2), 5.51 (d, 1H, J=1 Hz, =CH_2), 6.12 (d, 1H, J=1 Hz, =CH_2), and 7.72 (m, 4H, Ar H).

The other from the slower-moving band was a white solid (adduct **3b**, 82.0% yield): mp 90—92 °C. Recrystallization from cyclohexane gave colorless needles: mp 93—95 °C; IR (KBr) 3500 (OH), 1770, 1725 (shoulder), and 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.26 (t, 3H, J=7 Hz, CH_3), 1.45 (s, 3H, CH_3), 2.12 (m, 2H, CH_2), 3.41 (s, 1H, OH, exchangeable with D_2O), 3.78 (t, 2H, J=7 Hz, CH_2), 4.11 (q, 2H, J=7 Hz, OCH_2), and 7.73 (m, 4H, Ar H). Found: C, 62.01; H, 5.89; N, 5.24%. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81%.

Reaction of *N*-(Hydroxymethyl)phthalimide (1) with Acrylonitrile (5a) or Methacrylonitrile (5b). After the reaction of **5a** with two equivalents of **1** under the same reaction conditions, products were separated by column chromatography. The major product was **6a** (89.7% yield based on **5a**): mp 195—196 °C (lit,[5] 193 °C). Others are by-products formed from excess **1**: phthalimide (23% yield), bis(phthalimide)methane (1% yield); mp 227—229 °C (lit,[6] 226 °C), and bis(phthalimidemethyl) ether (2% yield); mp 205—207 °C (lit,[7] 207—209 °C).

With **5b** and two equivalents of **1**, the reaction proceeded in a similar manner giving rise to the formation of **6b** along with the by-products from **1** as in the case of **5a**. The yield of **6b** was 83.6% on the basis of **5b**: mp 159—161 °C; IR (KBr) 3390 (NH), 1775, 1720 (shoulder), and 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.95 (s, 3H, CH_3), 5.27 (d, 2H, J=6 Hz, CH_2), 5.38 (s, 1H, =CH_2), 5.74 (s, 1H, =CH_2), 6.85 (br s, 1H, NH), and 7.72—7.87 (m, 4H, Ar H); ^{13}C NMR ($CDCl_3$) δ=18.4 (CH_3), 42.8 (CH_2), 120.7 (=CH_2), 123.5 (Ar C), 131.8 (Ar C), 134.2 (Ar C), 139.2 (=C), 167.4 (imide C=O), and 167.6 (C=O). Found: C, 64.06; H, 4.78; N, 11.65%. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47%.

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