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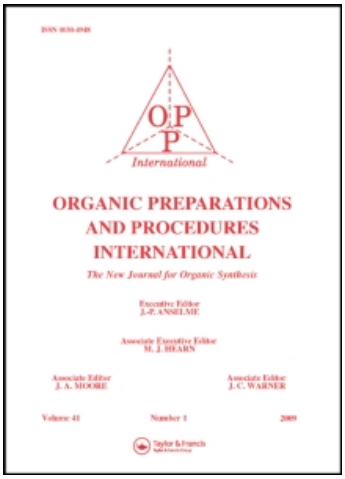


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# THE PREPARATION OF OLEFINIC DERIVATIVES OF PHTHALIMIDE AND THEIR USE AS THE PRECURSORS FOR HOMOALLYLIC AMINES

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**To cite this Article** Bergmann, E. D. and Migron, Y.(1976) 'THE PREPARATION OF OLEFINIC DERIVATIVES OF PHTHALIMIDE AND THEIR USE AS THE PRECURSORS FOR HOMOALLYLIC AMINES', Organic Preparations and Procedures International, 8: 2, 75 — 80
**To link to this Article: DOI:** 10.1080/00304947609355592
**URL:** http://dx.doi.org/10.1080/00304947609355592

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ORGANIC PREPARATIONS AND PROCEDURES INT. 8(2), 75-80 (1976)

# THE PREPARATION OF OLEFINIC DERIVATIVES OF PHTHALIMIDE AND THEIR USE AS THE PRECURSORS FOR HOMOALLYLIC AMINES

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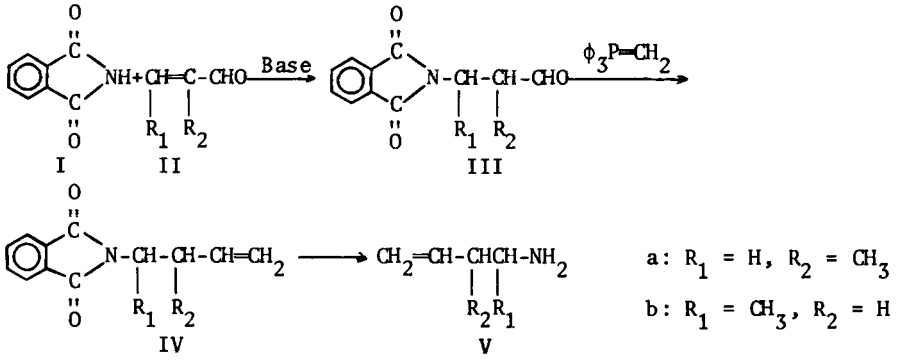
4-Amino-1-butene (V,$R_1$=$R_2$=H) has been prepared by the hydrazinolysis of 4-phthalimido-1-butene (IV,$R_1$=$R_2$=H)[1]. Although derivatives of IV can be prepared by the Wittig reaction with phthalimidopropanals (III), the synthesis of these aldehydes involves some tedious steps. For example, hydroformylation of 3-phthalimido-1-propene yields a difficulty separable mixture of two aldehydes[2]. The preparation of 3-phthalimidobutanal from phthalic anhydride and 3-aminobutyric acid[3] requires several steps while condensation of phthalimide with the corresponding α,β-unsaturated aldehydes in ethanol and EtONa affords impure products.

We now report the synthesis of Va as shown below




[+] Deceased April 5, 1975



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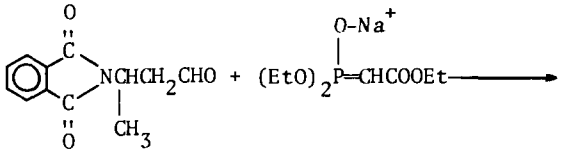
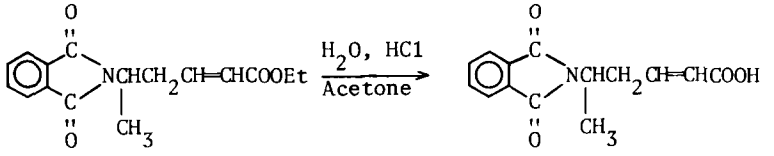
2-Methyl-3-phthalimidopropanal (IIIa) and 3-phthalimidobutanal (IIIb) were obtained through the reaction of phthalimide and methacrolein (IIa) and crotonaldehyde (IIb) respectively in the presence of a basic catalyst. Triton B or trimethylbenzylammonium methylate in DMF afforded the best yield of aldehyde free of any impurities. N-(2-Methyl-3-butenyl)phthalimide (IVa) and N-(1-methyl-3-butenyl)phthalimide (IVb) were prepared by the Wittig reaction using IIIa and IIIb and methylenetriphenylphosphorane. Experiments were conducted below 10° since the aldehydes are extremely sensitive to bases and may decompose to phthalimide and IIa or IIb respectively. The yield of olefins decreased considerably when the mixtures were allowed to stand - even at 0° - for several hours. It is notable that the yields increased when the phosphorane was added to the aldehyde solution instead of the usual reverse procedure. Products were separated on preparative scale by dry chromatography[5] on silica gel with chloroform as solvent. 2-Methyl-3-butenylamine (Va) was obtained from IVa by hydrazinolysis[6] (the corresponding amine 1-methyl-3-butenylamine (Vb) was not prepared). The use of sodium triethyl phosphonoacetate instead of methylenetriphenylphosphorane yielded <u>trans</u> ethyl 5-phthalimido-2-hexenoate (VII). 5-Phthalimido-2-hexenoic acid (VIII) was obtained from VII by



IVb VI



VII VIII



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acidic hydrolysis (basic hydrolysis cleaves the imidic bond). However, ethyl 3-methyl-5-phthalimido-2-pentenoate (IX) could not be obtained from 4-phthalimidobutane-2-one (X) by the same procedure owing to the rapid decomposition of X to phthalimide and butene-2-one.

## EXPERIMENTAL

2-Methyl-3-phthalimidopropanal (IIIa).- To a stirred and preheated solution of phthalimide (29.4g, 0.2 mole) and methacrolein (14g, 0.2 mole) in DMF, was added portionwise at 80° 2.5 ml triton B (40% in methanol) by means of a pipette with the tip sunk into the solution. Addition lasted 7 min., after which stirring was continued at the same temperature for 15 min. The reaction mixture was cooled, neutralized with 3 ml glacial acid, poured into water, and extracted with methylene chloride. The organic phase was washed with water, cold aqueous NaOH, dried ($MgSO_4$) and the solvent evaporated. The last traces of solvent were removed in vacuum. The residue afforded 25.8g (59%) of an amorphous colorless powder, mp. 84-5° (from isopropanol). Since large losses occurred during recrystallization, the crude substance was used for the next step. Mass spectrum (80eV) m/e 217 ($M^+$). NMR ($CDCl_3$): δ 9.7 (d, J = 2Hz, 1H, O=C-H), 7.8 (m, 4H, ArH), 3.93 (m, 2H, AB of ABX pattern, $CH_2$-N), 3.0 (m, 1H, CH-C=O), 1.3 (d. J = 7Hz, 3H, C-$CH_3$). IR (Nujol): 1705 (imide C=O, aldehyde C=O), 1780 $cm^{-1}$ (imide C=O).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.49.
Found: C, 66.16; H, 5.09; N, 6.61.

3-Phthalimidobutanal (IIIb).- IIIb was prepared as described for IIIa, except for the use of 2.5 ml trimethylbenzylammonium methylate (40% in methanol) instead of triton B which gave lower yields. There was obtained 27.5g (62% yield) of colorless crystals, mp. 109-111 (from isopropanol). Recrystallization is unnecessary for the continuation of the synthesis.



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Mass spectrum (80eV) m/e 217 ($M^+$). NMR ($CDCl_3$): δ 9.7 (t, J = 2Hz, 1H, O = C<u>H</u>), 7.75 (m, 4H, ArH), 4.83 (sext. J = 7Hz, 1H, CH-N), 3.1 (m, 2H, AB of ABX pattern, $C\underline{H}_2$-C = O), 1.65 (d, J = 7Hz, 3H, $C\underline{H}_3$). IR (Nujol): 1710 (aldehyde C=O), 1725, 1775 $cm^{-1}$ (imide C=O).

<u>Anal.</u> Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.49

Found: C, 66.20; H, 5.29; N, 6.70.

<u>N-(2-Methyl-3-butenyl)phthalimide (IVa)</u>.- A hexane solution of butyllithium (15%, 12.5 ml, 0.02 mole) was added with stirring under argon to a precooled suspension of triphenylmethylphosphonium bromide (7.14g, 0.02 mole) in dry THF (100 ml.). After 1 hr. at 0° the red-orange solution was added slowly (20 min.; internal temperature 0-5°) to a solution of IIIa (4.34g, 0.02 mole) in dry THF (100 ml). The heavy slurry was then stirred at room temperature for 30 min., water (20 ml) was added and the clear solution refluxed for 30 min. The THF was evaporated, water was again added and the reaction mixture extracted with methylene chloride. The residue was purified by dry chromatography (absorbent: Woelm silica gel for dry chromatography, ratio of absorbent to reaction mixture is 15-20:1, eluent: chloroform) to give colorless needles in 58% yield; mp. 68° (from cyclohexane). Mass spectrum (70eV) m/e 215 ($M^+$). NMR ($CDCl_3$); δ 7.8 (m, 4H, ArH), 5.7 (m. 1H, C = C<u>H</u>), 4.9 (m, 2H, C = $C\underline{H}_2$), 3.6 (d, J = 8Hz, 2H, $C\underline{H}_2$-N), 2.75 (m, 1H, H<u>C</u>-C = C), 1.03 (d, J = 7Hz, 3H, $C\underline{H}_3$). IR (Nujol): 1710, 1775 (C = O), 1645 $cm^{-1}$ (C = C).

<u>Anal.</u> Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.04; N, 6.51.

Found: C, 72.25; H, 5.71; N, 6.58.

<u>N-(1-Methyl-3-butenyl)phthalimide (IVb)</u>.- IVb was prepared in the same manner as IVa. Triphenylmethylphosphonium bromide (3.57g, 0.01 mole), butyllithium (0.01 mole), and IIIb (2.17g, 0.01 mole) afforded 2.3g of the crude mixture, which was separated by dry chromatography (conditions as



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IVa) to give 40% of a colorless liquid, bp. 100-110° (0.2 mm). Mass spectrum (70eV) m/e 215 ($M^+$). NMR ($CDCl_3$): δ 7.8 (m, 4H, ArH), 5.7 (m, 1H, HC = C), 5.0 (m, 2H, $H_2C$ = C), 4.5 (m, 1H, HC-N), 2.7 (m, 2H, $CH_2$-C = C), 1.6 (d, J = 7Hz, 3H, $CH_3$). IR (SC): 1710, 1778 $cm^{-1}$ (C = O).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.04; N, 6.51.

Found: C, 72.74; H, 6.02; N, 6.37.

5-Phthalimido-2-hexenoic acid (VIII).- A solution of ethyl triethylphosphonoacetate (2.24g, 0.01 mole) in DMF (50 ml) was added at room temperature to a suspension of NaH (0.4g, 60% in paraffin, 0.01 mole) in dry DMF (50 ml). The suspension was stirred until the evolution of hydrogen ceased and IIIb(2.17g, 0.01 mole) in dry DMF (50 ml) was added rapidly. The reaction mixture was heated at 80° for 1 hr., then cooled, poured into 5% aqueous HCl, and extracted with methylene chloride. The organic layer was washed with water, dried ($MgSO_4$), and evaporated, to yield trans ethyl 5-phthalimido-2-hexenoate (VII) as an oil.

NMR ($CDCl_3$): δ 7.75 (m, 4H, ArH), 6.80 (m, 1H, CH = C-COO), 5.75 (d, J = 16Hz, 1H, C = CHCOO), 4.45 (m, 1H, CH-N), 4.10 (q, J = 7Hz, 2H, $CH_2$-O), 2.96 (m, 2H, C = C-$CH_2$), 1.55 (d, J = 7Hz, 3H, N-C-$CH_3$), 1.25 (t, J = 7Hz, 3H, $OCH_2CH_3$). The crude ester VII was hydrolyzed without purification. The solution of VII in acetone (50 ml), water (35 ml), and conc. HCl (15 ml) was heated under reflux for 1.5 hrs., the acetone was evaporated and the organic material extracted with methylene chloride, washed with aqueous $NaHCO_3$, acidified with conc. HCl to pH 2-3, dried ($MgSO_4$) and the solvent evaporated. The residue (1.4g, 53% from IVb crystallized on standing, mp. 115-116° (from aqueous ethanol). NMR ($CDCl_3$): δ 7.7 (narrow m, 4H, ArH), 6.7 (m, 1H, CH = C-COOH), 5.73 (d, J = 16Hz, 1H, C = CH-COOH), 4.45 (m, 1H, CH-N), 2.90 (m, 2H, $CH_2$-C=C), 1.60 (d, J = 7Hz, 3H, C-$CH_3$). IR (Nujol): 3200-2850 (carboxylic OH and CH), 1778, 1768 (imide C = O),



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1700 $cm^{-1}$ (carboxylic C = O).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.68; H, 5.01; N, 5.40.
Found: C, 64.66; H, 5.04; N, 5.14.

2-Methyl 3-butenylamine (Va).- A solution of IVa (10.7g., 0.05 mole) and hydrazine hydrate (2.5g., 0.05 mole) in 95% aqueous ethanol (200 ml) was heated under reflux[6] for 2.5 hrs., (2-Methyl-3-butenylammonium phthalazinate started to precipitate after 30 min). The reaction mixture was cooled, acidified with conc. HCl to pH 2-3, filtered and the filtrate concentrated. Filtration was repeated and water was added to the filtrate. This procedure was repeated once more until a clear solution was obtained. Finally the mixture was evaporated to dryness and the residue basified with 50% aqueous NaOH. The upper layer, viz. the amine Va, separated as a liquid (2.5g, 60% yield), bp. 70-75° (∿700 mm). Mass spectrum: m/e 85 ($M^+$). NMR ($CDCl_3$): δ 5.7 (m, 1H, $CH = CH_2$), 5.2 (m, 1H, CH = CH trans to H), 5.0 (m, 1H, CH = CH cis to H), 2.65 (d, J = 6.5Hz, 2H, $CH_2$-N), 2.15 (m, 1H, $\rangle CH$), 1.1 (d, J = 6Hz, 3H, C-$CH_3$).

Anal. Calcd for $C_5H_{11}N$: C, 70.58; H, 12.94; N, 16.47.
Found: C, 70.47; H, 12.80; N, 16.25.

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(Received December 29, 1976; in revised form April 27, 1976)



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