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Microwave-assisted synthesis of *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide

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A new and efficient synthesis of a naturally occurring amide alkaloid, *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide isolated from the roots of *Piper nigrum* has been described involving a total of nine steps. Octanal and 2-bromoacetic acid have been used as the starting materials.

Keywords: amide alkaloid; dehydrohalogenation; modified Wittig reaction; microwave irradiation; ionic liquid

1. Introduction

Alkaloids are highly reactive substances with biological activity in low doses. Many plant extract and essential oils possess larvicidal activity against various mosquito species. Isobutyl amide moiety appears to be essential for toxicity against mosquito larvae (Ikan, 2007). Certain plant-derived compounds were found to be highly effective against insecticide resistant insect pests. For example, *Piper nigrum* fruits-derived guineensine exhibits remarkable lethal activity against a pyrenthrin-resistant strain of *Musca domestica*. The insecticidal constituents of piper fruits are *N*-isobutyl amide alkaloids such as dihydropipercide, guineensine, pellitorine and pipercide. These isobutyl amides have knock down activity against adults of *Callosobruchus chinensis*, *M. domestica* and *Periplaneta americana*. Most of the already known compounds isolated from dried seeds of *P. nigrum L.* exhibited toxicity against larvae of *Aedes aegypti* (I.-K. Park, Lee, Shin, J.-D. Park, & Ahn, 2002).

Piper nigrum (Williamson, 2002) is a climbing perennial shrub, rooting at the stem nodes with ovoid or globose fruits. It is widely distributed in the tropical and subtropical regions of the world. Pepper (fruits of *P. nigrum*) is one of the most popular spices in the world and has been used as a folk medicine due to its many physiological activities, e.g. stimulation of the central nervous system, analgesic and antipyretic activities (Lee, Shin, & Woo, 1984; Thampuran & Vijayan, 2000). It is much employed as an aromatic stimulant in weakness following fevers, coma, etc. as a stomachic in cholera, dyspepsia, flatulence indigestion, diarrhoea and various other gastrointestinal ailments. It has bacteriostatic, fungistatic, anti-inflammatory and rubefacient properties.

Phytochemical investigations of the roots of *P. nigrum L.* resulted in the isolation of 39 amides (Wei et al., 2004). In the total synthesis of sylvamide, an *N*-isobutyl alkaloid

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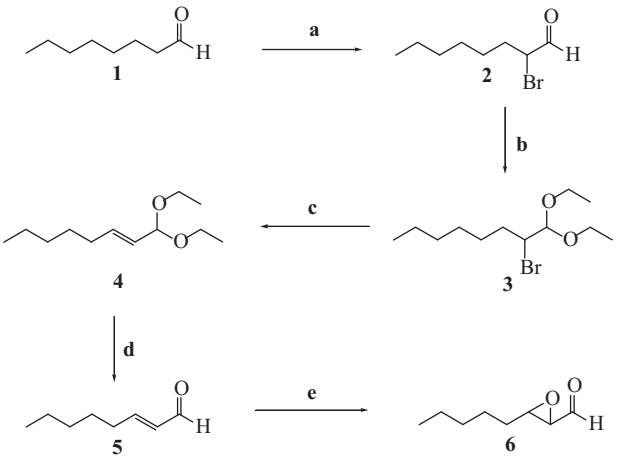


Scheme 1. (a) Br_2, $CaCO_3$, $CHCl_3$, 36 h, stir; (b) C_2H_5OH, [bmim]HSO_4, MWI 160 W (5 min); (c) $NaOC_2H_5$, DMSO, 120°C, 16 h; (d) [bmim]HSO_4, MWI, 8 min; (e) H_2O_2, pH 8–8.5, 2 h.

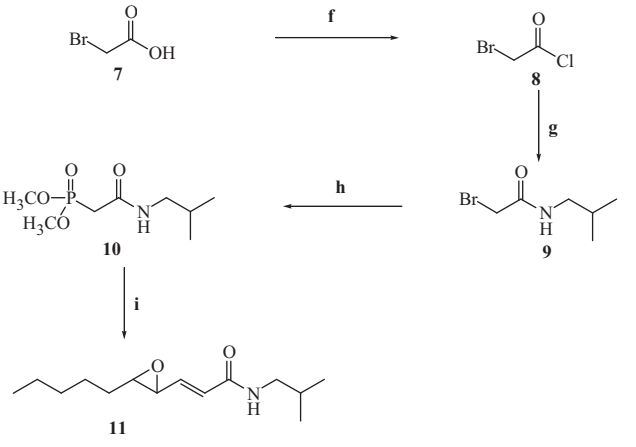
(Banerji & Pal, 1983) *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide was prepared as an intermediate.

2. Results and discussion

In continuation of our study utilising microwave energy as a source of heat in organic synthesis (Gupta, Sonu, Kad, & Singh, 2007; Kad, Kaur, Bansal, & Singh, 1996; Kad, Kaur, Bhandari, Singh, & Kaur, 2003; Kad, V. Singh, Kaur, & J. Singh, 1997; Singh, Gupta, Kad, & Kaur, 2006; Singh, Sharma, Kad, & Chhabra, 1997; Singh, Sharma, & J. Singh, 2008, 2009), we report herein, a simple synthesis of *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide. Retrosynthetic analysis revealed the need of oct-2-enal as the starting material for the synthesis of title compound.

Our first attempt to synthesise oct-2(*E*)-enal from 1,1-diethoxyhexane and ethyl vinyl ether in the presence of K-10 clay (Fishman, Klug, & Shani, 1981) was unsuccessful as the yield of the required product was very poor. Therefore, shifting to another route, we decided to synthesise oct-2(*E*)-enal by the allylic oxidation of alkene using 2-octene and SeO_2, *t*-BuOOH (Payne, 1960) or SeO_2/H_2O_2 (MWI) or SeO_2/UHP (MWI) (Manktala, Dhillon, & Chhabra, 2006), but none results in the isolation of desired product.

Finally, the oct-2(*E*)-enal was synthesised using protection and dehydrohalogenation strategy starting from octanal (Scheme 1). Bromination (Heilbron, Jones, Richardson, & Sondheimer, 1949) of octanal (**1**) using bromine and $CaCO_3$ in $CHCl_3$ at room temperature (10–15°C) furnished 2-bromooctanal (**2**) in 94% yield. Compound (**2**) when treated with [bmim]HSO_4 and ethanol under microwave irradiation gave 2-bromo-1, 1-diethoxyoctane (**3**) in 85% yield. Dehydrohalogenation (Nelson & Mash, 1986) of 2-bromo-1,1-diethoxyoctane (**3**) using sodium ethoxide in DMSO at 120°C furnished 1,1-diethoxyoct-2-ene (**4**). Compound (**4**) when treated with [bmim]HSO_4 under microwave irradiation afforded oct-2(*E*)-enal (**5**) in 84% yield. Epoxidation (Payne, 1959) of oct-2(*E*)-enal (**5**) with 30% H_2O_2 at pH 8–8.5 provided 2,3-epoxyoctanal (**6**) in 88% yield. 2-Bromoacetic acid (**7**) on heating with PCl_3 gave 2-bromoethanoylchloride (**8**). The formation of the product was indicated by the appearance of solid residue at the bottom and the product formed was used as such (Scheme 2). Reacting isobutylamine with



Scheme 2. (f) PCI_3, heat; (g) H_2N^iBu, $(C_2H_5)_3N$, dry DCM, 0°C, 18 h; (h) $(CH_3O)_3P$, MWI 640 W (10 min); (i) **6**, NaH, anhydrous Al_2O_3, stir for 3 h.

2-bromoethanoylchloride (**8**) in the presence of triethylamine and dry DCM at 0°C gave *N*-isobutyl-2-bromoethanamide (**9**) in 65% yield. Microwave irradiation of a mixture of *N*-isobutyl-2-bromoethanamide (**9**) and trimethylphosphite at 640 W for 10 min afforded phosphonate (**10**) in 75% yield. Modified Wittig reaction of phosphonate (**10**) (Wadsworth & Emmons, 1961) and 2,3-epoxyoctanal (**6**) using NaH doped on anhydrous Al_2O_3 gave *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide (**11**) in 47% yield.

Spectral data of the synthesised compound were compatible with that reported in literature (Wei et al., 2004).

3. Experimental

IR spectra were recorded on a Perkin Elmer model 1430 spectrometer. ^{1}H-NMR spectra were recorded using Varian EM-360 (60 MHz) spectrometer. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. Microwave-assisted reactions were carried out in LG MS-194A (800 W) domestic microwave oven.

3.1. *2-Bromooctanal (2)*

Octanal (**1**, 7.0 g, 54.6 mmol) in chloroform (22 mL) together with finely powdered calcium carbonate (4.34 g) was taken in a round bottom flask. The reaction mixture was stirred at room temperature (10–15°C) and a solution of bromine (8.68 g, 10.8 mmol) in $CHCl_3$ (8 mL) was added dropwise. After being stirred until the colour of the reaction mixture changes from orange to white, the mixture was filtered and solvent removed under reduced pressure to yield 2-bromooctanal (**2**, 10.4 g, 94%).

IR (neat)/ν_{max} cm^{-1}: 2927, 2857, 1730, 610. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 9.5 (d, 1H, $J = 2$ Hz, –CHO), 4.2 (m, 1H, –CHBr–), 1.6–1.1 (m, 10H, saturated methylene protons), 0.9 (t, 3H, $J = 6$ Hz, –CH_3).

3.2. *2-Bromo-1,1-diethoxyoctane (3)*

Ionic liquid [bmim]HSO_4 (0.1 g, 0.42 mmol) was added to a mixture of 2-bromooctanal (**2**, 0.50 g, 2.5 mmol) and ethanol (0.23 g, 5 mmol) taken in a conical flask which was covered with a polythene film and exposed to MWI at 160 W for 5 min non-continuously with 30 s

heating and cooling time. The reaction mixture was extracted with diethyl ether (2×15 mL). Unreacted aldehyde was removed by shaking with alkaline hydrogen peroxide solution and finally washed with water. The resulting solution was dried over anhydrous sodium sulphate. Evaporation of the solvent *in vacuo* provided pure 2-bromo-1,1-diethoxyoctane (**3**, 0.663 g, 85%).

IR (CCl_4)/ν_{max} cm^{-1}: 2925, 2856, 1110, 624. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 4.4 [d, 1H, $J = 6$ Hz, –CHBr–$CH(OC_2H_5)_2$], 3.4–3.1 [m, 5H, $2 \times$ –OCH_2 and –CHBr], 1.3–0.9 (m, 19H, saturated methylene and methyl protons).

3.3. *1,1-Diethoxyoct-2-ene (4)*

To a well-stirred solution of 2-bromo-1,1-diethoxyoctane (**3**, 2.0 g, 7.11 mmol) in DMSO (12 mL) at 120°C was added sodium ethoxide (1.50 g, 22 mmol) and the progress of the reaction was monitored by thin layer chromatography. The reaction mixture was poured into saturated NaCl solution (50 mL) after 16 h and extracted with diethyl ether (3×25 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Chromatography of the crude product on silica gel eluted with 10% ethyl acetate in hexane gave the desired product 1,1 diethoxyoct-2-ene (**4**, 0.639 g, 45% yield).

IR (CCl_4)/ν_{max} cm^{-1}: 3012, 2924, 2856, 1653, 1108. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 5.2 [d, 1H, $J = 6$ Hz, –$CH(OCH_2CH_3)_2$], 4.8 (dd, 1H, $J = 4$ Hz, $J = 12$ Hz, –CH_2–CH=CH–), 4.2–3.7 (m, 5H, $2 \times$ –OCH_2 and CH_2–CH=CH–), 1.5–0.9 (m, 17H, saturated methylene and methyl protons).

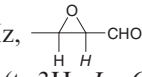
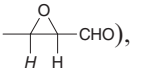
3.4. *Oct-2(E)-enal (5)*

Equimolar mixture of 1,1 diethoxyoct-2-ene (**4**, 2.0 g, 10 mmol), [bmim]HSO_4 (1.39 g, 10 mmol) and water (0.18 g, 10 mmol) were taken in a conical (50 mL) and exposed to microwave radiations (160 W) for 8 min non-continuously ($30 + 30s + \cdots$). The resulting mixture was allowed to cool and extracted with diethyl ether. Organic layer was washed with brine and finally dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure afforded crude aldehyde that was purified by column chromatography using ethyl acetate and hexane (0.5:9.5) as eluent to afford pure aldehyde (**5**, 1.07 g, 84%).

IR (neat)/ν_{max} cm^{-1}: 2960, 2734, 1690, 1643. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 9.4 (d, 1H, $J = 4$ Hz, –CHO), 6.8 (dd, 1H, $J = 4$ Hz, $J = 12$ Hz, –CH=CH–CHO), 6.2–5.9 (m, 1H, –CH=CH–CHO), 1.8–1.1 (m, 8H, saturated methylene protons), 0.9 (t, 3H, $J = 6$ Hz, CH_3).

3.5. *2,3-Epoxyoctanal (6)*

Totally, 30% H_2O_2 (1.70 g, 0.05 mol) and distilled water (12 mL) were taken in a three-necked round-bottom flask equipped with two additional funnels and standard electrode connected to a digital pH meter. The pH was adjusted between 8 and 8.5 by the addition of 0.2N NaOH and then oct-2(*E*)-enal (**5**, 1.0 g, 9.80 mmol) was added dropwise. The pH was maintained at 8–8.5 by the addition of alkali. After the complete addition of oct-2(*E*)-enal, the reaction mixture was stirred for an additional hour, saturated with sodium chloride and finally extracted with DCM (4×15 mL). Combined organic extracts were dried and evaporated *in vacuo* to give pure 2,3-epoxyoctanal (**6**, 1.22 g, 88%).

IR (neat)/ν_{max} cm^{-1}: 2959, 2848, 1728, 1252. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 9.1 (d, 1H, $J = 8$ Hz, –CHO), 3.4 (t, 1H, $J = 6.4$ Hz, ), 3.1 (m, 1H, ), 1.3–1.1 (m, 8H, saturated methylene protons), 0.9 (t, 3H, $J = 6$ Hz, CH_3).

3.6. *N-Isobutyl-2-bromoethanamide (9)*

2-Bromoethanoic acid (**7**, 6.12 g, 43.8 mmol) and distilled phosphorous trichloride (PCl_3) (2.0 g, 14.6 mmol) were heated in a round bottom flask till the evolution of HCl gas ceases. The acid chloride (**8**) thus prepared was decanted, dissolved in dry DCM (20 mL) and added dropwise to ice-cold mixture of triethylamine (4.0 g, 34.0 mmol) and isobutylamine (2.58 g, 35.0 mmol) in dry DCM (40 mL) taken in another round bottom flask. The reaction mixture was allowed to stir overnight. The product was then extracted with DCM (3×20 mL), washed with water (3×10 mL), brine and dried over anhydrous sodium sulphate. The solvent was evaporated under vacuum to afford *N*-isobutyl-2-bromoethanamide (**9**, 4.41 g, 65%).

IR ($CDCl_3$)/ν_{max} cm^{-1}: 3340, 2960, 2850, 1663, 604. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 5.6 (bs, 1H, –CONH–), 4.0 (s, 2H, $BrCH_2$–), 3.1 (d, 2H, $J = 6$ Hz, –$NHCH_2$–), 2.3–2.0 [m, 1H, –$CH_2CH(CH_3)_2$], 0.9 [d, 6H, $J = 8$ Hz, –$CH(CH_3)_2$].

3.7. *Isobutyl carbamoylmethyl phosphoric acid dimethyester (10)*

A mixture of trimethylphosphite (0.32 g, 2.56 mmol) and *N*-isobutyl-2-bromoethanamide (**9**, 0.5 g, 2.56 mmol) was taken in a conical flask covered with a polythene film and irradiated with microwaves at 640 W for 10 min ($30 + 30s + \cdots$) to afford isobutyl carbamoylmethyl phosphoric acid dimethyl ester (**10**, 0.426 g, 75%).

IR (nujol)/ν_{max} cm^{-1}: 3343, 2956, 2847, 1645, 1264, 1106. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 5.4 (bs, 1H, –CONH–), 4.9 (s, 2H, –$POCH_2CO$–), 3.9 (s, 6H, $2 \times$ –OCH_3), 3.1 (d, 2H, $J = 6$ Hz, –$NHCH_2$–), 2.2–1.9 [m, 1H, –$CH(CH_3)_2$], 0.9 [d, 6H, $J = 6$ Hz, –$CH(CH_3)_2$].

3.8. *N-Isobutyl-4,5-epoxy-2(E)-decenamide (11)*

NaH (0.83 g, 34.58 mmol) was ground with basic alumina and phosphonate (**10**, 3.06 g, 16.16 mmol) till the evolution of the gas ceased. The reaction mixture was cooled and 2,3-epoxyoctane (**6**, 2.0 g, 13.8 mmol) was added dropwise to it. After the addition was complete, the reaction mixture was ground for another 2 h and left overnight. It was then extracted with diethyl ether (4×25 mL) and solvent evaporation followed by silica gel column chromatography with pet ether: ethyl acetate (4:1) as eluent afforded *N*-Isobutyl-4,5-epoxy-2(*E*)-decenamide (**11**, 1.65 g, 47%).

IR (nujol)/ν_{max} cm^{-1}: 3348, 2960, 2840, 1652, 1624, 1260, 1240. NMR ($CDCl_3$, 60 MHz) δ: 6.8 (d, 1H, $J = 14$ Hz, –CH=CH–CO–), 6.4 (dd, 1H, $J = 14$ Hz, $J = 6$ Hz, –CH=CH–CO–), 5.9 (bs, 1H, –OCNH–), 3.3 (t, 1H, $J = 6.4$ Hz, –OCHCH=), 3.1–2.9 (m, 1H, –CHO–), 2.8 (d, 2H, –$NHCH_2$–), 2.2–1.9 [m, 1H, –$CH(CH_3)_2$], 1.5–1.2 (m, 8H, saturated methylene protons), 1.1–0.9 (m, 9H, $3 \times CH_3$).

4. Conclusion

In conclusion, we have achieved a new and efficient synthesis of a naturally occurring amide alkaloid, *N*-isobutyl-4,5-epoxy-2(*E*)-decenamide isolated from the roots of *P. nigrum*, starting from octanal (**1**) and 2-bromoacetic acid (**7**). The key steps in the synthesis involved the microwave induced acetalisation of 2-bromooctanal (**2**) in ionic liquid [bmim]HSO_4, deprotection of 1,1-diethoxyoct-2-ene (**4**) using microwave energy and ionic liquid [bmim]HSO_4 and solid supported modified Wittig reaction of (**6**) and (**10**) to afford the title compound.

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