Gas-phase pyrolysis of N-alkoxyphthalimides to functionally substituted aldehydes: kinetic and mechanistic study

Alya M. Al-Etaibi,[a] Nouria A. Al-Awadi,[b]* Maher R. Ibrahim,[b] and Yehia A. Ibrahim[b]

[a]*Natural Science Department, College of Health Science, Public Authority for Applied Education and Training, Kuwait*
[b]*Chemistry Department, Faculty of Science, Kuwait University, P.O. Box 5969, Safat 13060, Kuwait*
E-mail: n.alawadi@ku.edu.kw

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.a13

Abstract
Flash vacuum Pyrolysis (FVP) of primary N-alkoxyphthalimides at 400-500 °C and 0.02 Torr gave functionally substituted aldehydes. A mechanism of this pyrolytic transformation was proposed based on the kinetic data and product analysis.

Keywords: FVP, N-alkoxyphthalimides, aldehydes, kinetics, reaction mechanism

Introduction

Substituted aldehydes and ketones are important intermediates in pharmaceutical and cosmetic industries,[1-3] While synthetic approaches to simple aldehydes are well established,[4] synthetic approaches to functionally substituted ones are not. FVP has been used in straightforward synthesis of many organic compounds which are not readily obtainable from reactions in solution. We have combined mechanistic and kinetic investigations to probe the gas-phase pyrolytic reaction in the synthesis of a wide rang of organic compounds.[5-8] In this work we wish to report further application of FVP in organic synthesis by describing a possible route for conversion of alkyl halides via their corresponding N-alkoxyphthalimides to functionally substituted aldehydes.

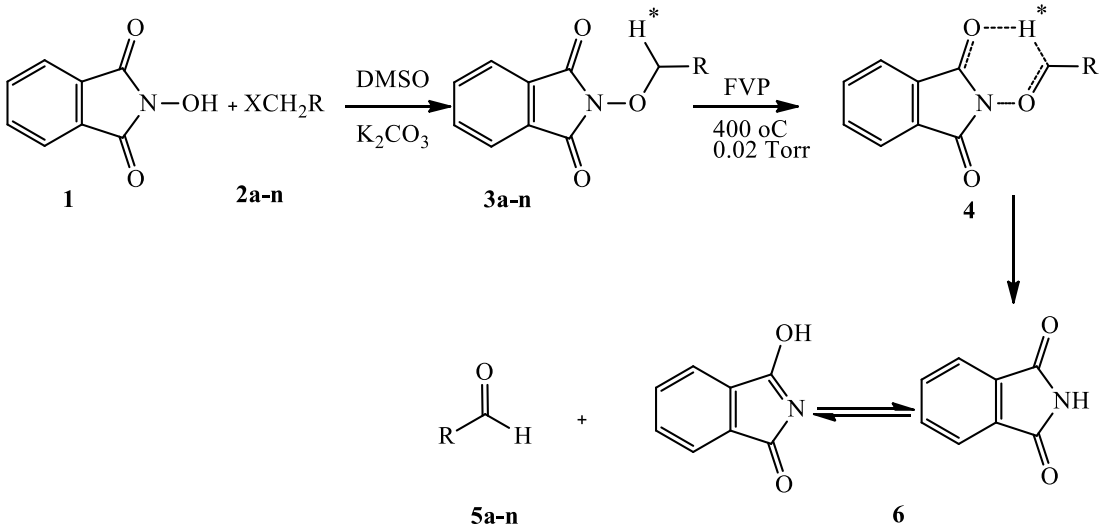
Results and Discussion

Synthesis

N-Hydroxyphthalimide **1** was reacted with alkyl halides **2a-n** to produce the corresponding *N*-alkoxyphthalimides **3a-n**, some of which are new compounds.

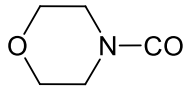
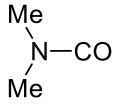
Pyrolysates and mechanism of pyrolytic reactions

Reaction products from FVP of N-alkoxyphthalimides **3a-n** were obtained at 400-500 ºC and 0.02 Torr and were characterized as the corresponding functionally substituted aldehydes **5a-n** and phthalimide **6 (**Scheme 1).

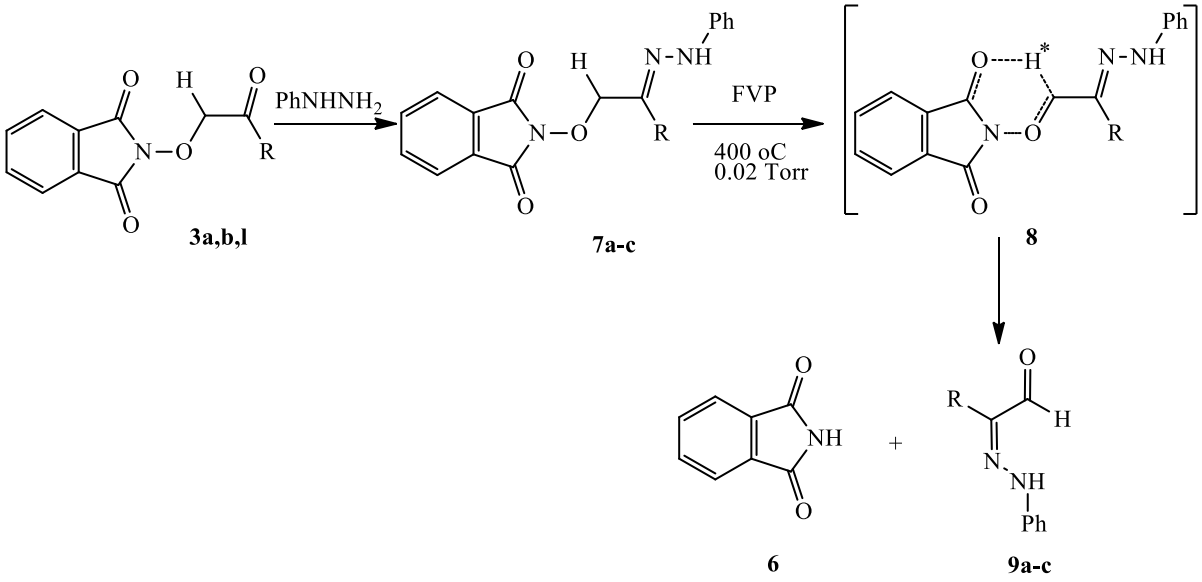


Scheme 1

Table 1. Products of FVP of **3a-n,** and % yield

Cpd	**R**	% Yield (FVP)		Temp. ºC
		5a-n	**6**	
3a	CH_3CO	14	60	400
b	C_6H_5CO	46	46	400
c	CH_3COCH_2	18	67	400
d		13	49	500
e		14	45	500
f	C_2H_5OCO	22	57	400
g	NC	12	74	400
h	*p*-$CH_3C_6H_4$	28	61	500
i	*p*-NCC_6H_4	32	60	500
j	*p*-ClC_6H_4	27	63	500
k	C_6H_5	38	50	500
l	*p*-$CH_3OC_6H_4CO$	49	50	400
m	*p*-ClC_6H_4CO	38	52	400
n	*p*-$O_2NC_6H_4CO$	32	58	500

The pyrolysates were qualitatively analyzed by HPLC, yields of each products was calculated by ^{1}H NMR (Table 1). The possible mechanistic route for the formation of **5** and **6** involves semiconcerted six-membered transition state **4**, it is to be noted that substituted aldehydes **5a-n** and phthalimide **6** are the only identifiable products isolated from this pyrolytic reaction. We have extended this approach for the synthesize of functionally substituted aldehydes, so *N*-acyloxymethoxyphthalimide **3a,b** and **l** were converted to phenylhydrazones **7a-c** this accomplished by the reaction with phenylhydrazine (scheme 2). FVP of **7a-c** at 400 ^{o}C and 0.02 Torr resulted in substituted glyoxal-2-phenylhydrazones **9a-c** and phthalimide **6**. Increasing the pyrolysis temperature to 500 ^{o}C led to decomposition of compounds **9a-c** yielding aniline, and the corresponding nitriles. This pyrolytic reaction provides new access for the synthesis of aldehydes **9a-c.** The literature shows only two synthetic methods to prepare **9a**.[9]



Scheme 2

Table 2. Products of FVP of **7a-c** and % yields

Cpd	**R**	% yield (FVP)		Temp. ^{o}C
		6	**9a-c**	
7a	CH_3	55	45	400
b	C_6H_5	55	38	400
c	*p*-$CH_3OC_6H_2$	57	40	400

Kinetic studies

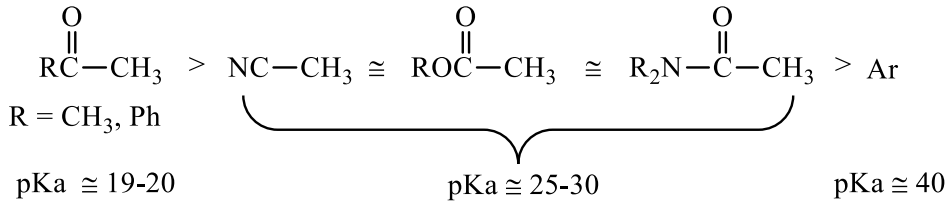
In the static reactor system, each substrate behaved well kinetically and gave excellent and reproducible first-order rate coefficients with linearity up to 95% reaction and with no deviation in the Arrhenius plots. Since six fold changes in the amount of substrate used per kinetic run

gave no significant change in rate coefficient, these reactions were deemed to be first-order process. The homogeneity of the reaction was tested by comparing the kinetic rate using an empty reaction vessel with that of similar vessel packed with glass helices, this increase in the surface to volume of approximate nine fold has not affected the kinetic rate. The kinetic data of the pyrolytic gas-phase elimination reaction of the N-alkoxyphthalimides under study are given in (Table 2). Each rate constant at any given temperature represents an average of two values obtained in two separate kinetic runs conducted at the same temperature. The agreement among the values at the rate constants in each run is within ± 2%. Each kinetic run was monitored until 90-95% of the reaction was completed. Arrhenius plots were linear over the studied temperature and reaction range.

Molecular reactivity

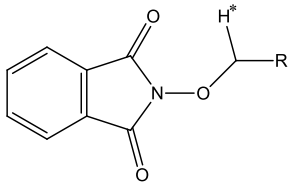
According to the pyrolysate of the pyrolytic reaction of the *N*-alkoxyphthalimides **3a-n** which eliminates to aldehydes **5a-n** and phthalimide **6**, a mechanistic pathway has been suggested as shown in (scheme 1), this involves a semiconcerted process with six-membered transition state 4, accordingly this reaction should be aided by greater electron- withdrawal from R, since this will increase the acidity of the hydrogen atom involved in the transition state which will facilitate the C-H* bond breaking. Rate coefficients presented in Table 2 shows that the most reactive N-alkoxyphthalimides is **3a** (R = -$COCH_3$) with rate coefficient of 4.62 s^{-1} at 500 K. This is 5.8 x 10^6 fold more reactive than the least reactive alkoxyphthalimide **3k** (R = C_6H_5). The analysis of the relative contribution to molecular reactivity from the polarization of the C-H* bond involved in the transition state explains this dramatic drop in the reactivity of the pyrolytic elimination of aldehyde between **3a** and **3k**, this attributed to the big difference in the acidity of the hydrogen atom of the two compounds.

The acidity of this hydrogen atom [H*] in substrates **3a-k** increases from X = RCO > CN ≅ CO_2R ≅ $CONR_2$ > Ar in parallel comparison with the acidity of the following carbon acids.[10] (Scheme 3)



Scheme 3

Table 3. Rate coefficient (k/s^{-1}) and Arrhenius parameters of compounds **3a-k**



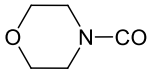
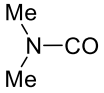
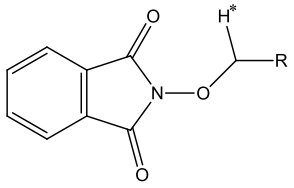
Cpd.	R	T/K	10^4k /s^{-1}	log A /s^{-1}	*E*a / k J mol^{-1}	K_{500K}/s^{-1}
3a	CH_3CO	382.95	0.174	18.3 ± 0.69	351.2 ± 13.2	4.62
		388.95	0.419			
		394.85	1.124			
		400.55	1.649			
		406.55	3.816			
		412.55	7.343			
		424.25	35.73			
3b	C_6H_5CO	359.75	1.015	11.6 ± 0.47	222.3 ± 9.00	2.36
		369.75	2.720			
		379.75	5.705			
		389.75	15.50			
		399.75	38.29			
3c	CH_3COCH_2	359.65	0.893	7.91 ± 0.43	151.5 ± 8.23	2.12×10^{-1}
		369.65	1.878			
		379.55	4.598			
		389.55	8.517			
		399.55	13.20			
		409.55	26.32			
3d		462.25	0.293	16.7 ± 0.20	188.1 ± 1.82	1.21×10^{-3}
		472.15	0.876			
		481.95	2.227			
		491.75	5.346			
		502.00	14.55			
		511.85	34.83			
3e		499.25	4.363	3.38 ± 0.04	64.46 ± 0.37	4.46×10^{-4}
		525.15	9.445			
		536.85	12.82			
		548.95	17.74			
		561.05	24.25			
3f	C_2H_5OCO	508.25	3.228	9.47 ± 0.13	181.3 ± 2.49	1.78×10^{-4}
		518.25	5.371			

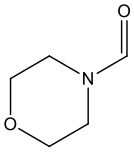
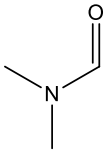
Table 3. Continued

Cpd.	R	T/K	104k /s-1	log A /s-1	Ea / k J mol-1	K500K/s-1
		528.25	7.250			
		538.25	14.39			
		548.25	30.55			
3g	NC	509.45	1.542	10.7 ± 0.62	205.5 ± 11.9	6.17×10^{-5}
		519.45	2.502			
		529.45	4.018			
		539.45	6.014			
		549.45	14.43			
		559.45	22.41			
		569.45	46.98			
3h	*p*-$CH_3C_6H_4$	550.85	0.923	9.84 ± 0.58	146.3 ± 6.43	3.63×10^{-6}
		562.75	2.020			
		574.95	3.615			
		586.75	5.782			
		598.55	10.89			
		610.65	24.39			
3i	*p*-NCC_6H_4	544.95	0.727	11.3 ± 0.47	160.6 ± 5.16	2.97×10^{-6}
		555.05	1.456			
		565.15	2.637			
		574.85	4.101			
		585.05	7.129			
		594.65	13.83			
		604.75	27.05			
3j	*p*-ClC_6H_4	554.05	0.680	12.2 ± 0.07	174.1 ± 0.83	1.12×10^{-6}
		565.95	1.462			
		578.05	3.167			
		589.95	6.581			
		601.75	13.49			
		614.05	26.97			
3k	C_6H_5	548.30	0.428	12.9 ± 0.50	182.0 ± 5.53	7.95×10^{-7}
		556.85	0.563			
		569.95	1.701			
		582.85	4.359			
		595.65	9.065			
		608.75	21.21			
		618.45	32.05			

Each compound of (**3a-k**) has a constant factor difference than the above CH* acids which is the *N*-oxyphthalimido group. The latter group should increase the acidity of the above carbon acids by a constant value. In absence of pKa value for our investigated compounds, we have correlated rate coefficient (at 500K) of the gase-phase pyrolysis of **3a-k** with the pKa of the above carbon acids (Table 3). The higher rate of pyrolysis of the amide **3d** over **3e** could be attributed to the less steric influence and the more inductive effect of the oxygen atom of the morpholide moiety in the former. The reaction pathway suggested to account for product formation is well rationalized by the kinetic investigation of these compounds.

Table 4. Rate coefficients of gas-phase pyrolysis of compounds **3a-k** at 500 K and pKa value of the corresponding carbon acids



Cod.	**R**	pKa	k_{500K}
3a	CH_3CO	19-20	4.62
3b	C_6H_5CO		2.36
3d		≅ 25-30	$1.21x10^{-3}$
3e			$4.46x10^{-4}$
3f	C_2H_5OCO		$1.78x10^{-4}$
3g	NC		$6.17x10^{-5}$
3h	p-$CH_3C_6H_4$	≅ 40	$3.63x10^{-6}$
3i	p-NCC_6H_4		$2.97x10^{-6}$
3j	p-ClC_6H_4		$1.12x10^{-6}$
3k	C_6H_5		$7.95x10^{-7}$

Conclusions

The present work describes a functional group transformation of alkyl halides via their corresponding *N*-alkoxyphthalimide to the corresponding aldehydes. It also provides a new access to functionally substituted aldehydes. Product analysis suggests a mechanistic pathway involves a six-membered transition states, kinetic data supports well this mechanism.

Experimental Section

General. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz super-conducting NMR spectrometer. Mass spectra were measured on VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalysis was performed on a LECO CH NS-932 Elemental Analyzer. The HPLC analysis was performed using a Metrohm HPLC (pump model 7091C and SHIMADZU SPD-10 UV/VIS detector), and Suppelco ABZ^{+} chromatography column (2.5 cm length and 4.6 mm ID, for 5 μm sample). The reactor used for kinetic and product analysis is a Chemical Data System (CDS) custom-made pyrolyzer consisting of an insulated aluminum-alloy block fitted with a platinum resistance thermocouple connected to a Comark microprocessor thermometer for reactor temperature read-out, accurate to < 0.5 °C. The alloy was chosen for its high thermal conductivity and low temperature gradient, and may be heated for up to 530 °C. The temperature of the reactor is controlled by means of a Eurotherm 093 precision temperature regulator to provide 0.1 °C incremental changes. The reaction tubes were Pyrex: 8 cm long for kinetic runs, and 12 cm for product analysis; with internal and outer diameters 1.5 cm and 1.7 cm, respectively, for both tubes.

Kinetic runs and data analysis

Stock solution (7 mL) was prepared by dissolving 5-10 mg of the substrate in acetonitrile to give a concentration of $1x10^{3}$ - $2x10^{3}$ ppm. An internal standard was then added, the amount of which was adjusted to give the desired peak area ratio of substrate to standard (2.5 : 1). The solvent and standard were selected to be stable under the conditions of pyrolysis, and because they do not interact or react with either substrate or product. The internal standard used in the present study was chlorobenzene and 1,3-dichlorobenzene. Each mixture was filtered before use to ensure a homogeneous solution.

The ratio of the amount of substrate with respect to the internal standard was calculated from the ratio of the substrate peak area to the peak area of the internal standard. The kinetic rate was obtained by tracing the rate of disappearance of the substrate with respect to the internal standard as follows: An aliquot part (0.2 mL) of each solution containing the substrate and the internal standard was pipetted into the pyrolysis tube, which was then cooled in liquid nitrogen and sealed at reduced pressure (0.28 mbar). The tube was then placed in the pyrolyzer for 6 minutes under non-thermal conditions (ambient temperature). A sample was then analyzed using HPLC with UV/VIS detector at wavelength, λ = 256 nm to calculate the standardization value (A_o). Several HPLC measurements were obtained with an accuracy ≥ 2%. The temperature of the pyrolysis block was then raised until ca 10% pyrolysis of the substrate was deemed to occur over 600 s interval. This process was repeated after each ca 10 °C rise in the reaction temperature until > 95% reaction was achieved. The relative ratios of the sample and the internal standard (A) at each reaction temperature was calculated for a minimum of two kinetic runs made at each of

these temperatures that were in agreement to within ± 2% in order to ensure reproducible values of (A). Treatment of the kinetic data has been detailed elsewhere.[5]

N-Alkoxyphthalimides 3a-n. General procedure

To a mixture of *N*-hydroxyphthalimide **1** (1.63 gm, 10 mmol), anhydrous potassium carbonate (0.5 gm) in dry DMSO (20 mL) was added the appropriate alkyl halides **2a-n** (10 mmol). The reaction mixture was stirred at room temoerature over night, and then ice water (50 mL) was added. The precipitate was then collected and crystallized from the proper solvent.

***N*-(2-Oxopropoxy)phthalimide (3a).** Colorless crystals from ethanol, mp 123-124 ºC (lit.[11] mp 120-122 ºC) yield (68%). MS: *m/z* = 219 (M^+, 60%), 174 (45%), 161 (100%), 147 (70%). ^{1}H NMR (DMSO-d_6) δ 7.88 (s, 4H), 4.88 (s, 2H, CH_2), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 203.2, 163.2, 135.4, 129.1, 123.8, 81.3, 27.2.

3.3.2 *N*-(2-Oxo-2-phenylethoxy)phthalimide (3b). White crystals from ethanol, yield (74%), mp 134-136 ºC (lit.[12] mp 135-136 ºC). MS: *m/z* = 281 (M^+,10%), 250 (20%), 222 (40%), 147 (50%), 105 (100%). ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 2H, *J* 7.8 Hz), 7.84-7.81 (m, 2H), 7.76-7.73 (m, 2H), 7.60 (t, 1H, *J* 7.4 Hz), 7.48 (t, 2H, *J* 7.6 Hz), 5.44 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 198.2, 168.2, 140.3, 139.7, 139.5, 134.4, 134.1, 133.4, 128.8, 84.1.

3.3.3 2-(3-Oxobutoxy)phthalimide (3c). White crystals from pet. Ether (60-80), yield (43%), mp 104-105 ºC. MS: *m/z* = 233 (M^+, 30%), 147 (100%). IR (KBr) 3069, 3008, 2970, 1727, 1630, 1373, 1184, 1130, 1032, 877, 703. ^{1}H NMR ($CDCl_3$) δ 7.87-7.84 (m, 2H), 7.79-7.76 (m, 2H), 4.52 (t, 2H, *J* 6.2 Hz), 2.98 (t, 2H, *J* 6.2 Hz), 2.28 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 205.3, 163.6, 134.5, 128.7, 123.6, 72.8, 42.0, 30.3. Anal. Calcd for $C_{12}H_{11}NO_4$ (233.2): C 61.80; H 4.75; N 6.01. Found: C 61.75; H 4.66; N 6.08.

***N*-(2-Morpholinyl-2-oxoethoxy)phthalimide (3d).** White crystals from ethyl acetate/petrolum ether (60-80), yield (58%), mp 176-178 ºC. LCMS: *m/z* = 291 (M + 1). IR (KBr) 3029, 2996, 2855, 1792, 1745, 1652, 1484, 1445, 1391, 1245, 1118, 1112, 1002, 696. ^{1}H NMR ($CDCl_3$) δ 7.87-7.7.84 (m, 2H), 7.79-7.77 (m, 2H), 4.85 (s, 2H, CH_2), 3.86-3.84 (m, 2H), 3.79-3.76 (m, 4H), 3.67-3.65 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 164.3, 163.0, 134.8, 128.7, 123.8, 75.8, 66.6, 66.5, 46.4, 42.3. Anal. Calcd for $C_{14}H_{14}N_2O_5$ (290.3): C 57.93; H 4.86; N 9.65. Found: C 57.72; H 4.86; N 9.55. [13]

***N*-(*N*,*N*-Dimethylcarboxamidomethoxy)phthalimide (3e).** White crystals from ethyl acetate/pet. ether (60-80), yield (58%), mp 157-158 ºC (lit.[14] mp 155-157 ºC). LCMS: *m/z* = 249 (M + 1). IR (KBr). 3029, 2935, 1724, 1649, 1381, 1186, 1133, 1183, 1017, 993, 874, 699. ^{1}H NMR ($CDCl_3$) δ 7.86-7.82 (m, 2H), 7.78-7.75 (m, 2H), 4.86 (s, 2H, CH_2), 3.25 (s, 3H, CH_3), 3.00 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$) δ 165.7, 163.1, 134.8, 128.8, 123.7, 75.7, 37.2, 35.6. Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.2): C 58.06; H 4.87; N 11.28. Found: C 58.00; H 4.86; N 11.19.

***N*-Ethoxycarbonylmethoxyphthalimide (3f)**. White crystals from ethanol, yield (75%), mp 97-98 ºC (lit.[15] mp 95-97 ºC). ^{1}H NMR ($CDCl_3$) δ 7.89-7.85 (m, 2H), 7.83-7.80 (m, 2H), 4.83 (s, 2H), 4.29 (q, 2H, *J* 7.2 Hz), 1.32 (t, 3H, *J* 7.2 Hz).

***N*-Cyanomethoxyphthalimide (3g).** White crystals from ethanol, mp 155-156 ºC, yield (64%). MS: *m/z* = 202 (M^+, 30%), 146 (15%), 132 (70%), 104 (100%). IR (KBr) 3076, 3022, 2980, 2228, 1771, 1740, 1462, 1417, 1356, 1322, 1183, 1127, 876, 706. ^{1}H NMR (DMSO-d_6) δ 7.93-7.89 (m, 4H), 5.24 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ 163.0, 135.6, 129.0, 124.1, 116.2, 63.2. Anal. Calcd for $C_{10}H_6N_2O_3$ (202.2): C 59.41; H 2.99; N 13.86. Found: C 59.38; H 2.86; N 13.79.

***N*-*p*-Methylbenzyloxyphthalimide (3h).** White crystals from ethanol, yield (87%), mp 193-194 ºC (lit.[16] mp 194 ºC). ^{1}H NMR ($CDCl_3$) δ 7.85-7.81 (m, 2H), 7.77-7.74 (m, 2H), 7.44 (d, 2H, *J* 7.8 Hz), 7.20 (d, 2H, *J* 7.8 Hz), 5.19 (s, 2H), 2.42 (s, 3H).

***N*-*p*-Cyanobenzyloxyphthalimide (3i).** White crystals from ethanol, yield (81%), mp 202-204 ºC (lit.[17] mp 199-200 ºC). ^{1}H NMR (DMSO-d_6) δ 7.90 (d, 2H, *J* 8.0 Hz), 7.88-7.84 (m, 4H), 7.75 (d, 2H, *J* 8.0 Hz), 5.28 (s, 2H).

***N*-*p*-Chlorobenzyloxyphthalimide (3j).** White crystals from ethanol, yield (86%), mp 138-140 ºC (lit.[18] mp 137-138 ºC). ^{1}H NMR ($CDCl_3$) δ 7.85-7.82 (m, 2H), 7.77-7.73 (m, 2H), 7.50 (d, 2H, *J* 8.3 Hz), 7.37 (d, 2H, *J* 8.3 Hz), 5.20 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 163.3, 135.3, 134.5, 132.0, 131.0, 128.6, 128.5, 123.4, 78.8.

***N*-Benzyloxyphthalimide (3k).** White crystals from ethanol, yield (81%), mp 143-144 ºC (lit.[19] mp 142-143 ºC). ^{1}H NMR ($CDCl_3$) δ 7.85-7.81 (m, 2H), 7.78-7.75 (m, 2H), 7.58-7.55 (m, 2H), 7.41-7.38 (m, 3H), 5.24 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 163.3, 134.3, 133.4, 129.7, 129.2, 128.6, 128.4, 123.5, 79.7.

***N*-(2-Oxo-2-*p*-methoxyphenylethoxy)phthalimide (3l).** White crystals from ethanol, yield (80%), mp 148-150 ºC. LCMS: *m/z* = 312 (M + 1). ^{1}H NMR ($CDCl_3$) δ 8.00 (dd, 2H, *J* 8.4, 1.6 Hz), 7.87-7.82 (m, 2H), 7.78-7.73 (m, 2H), 6.96 (dd, 2H, *J* 8.4, 1.6 Hz), 5.39 (s, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 190.7, 164.2, 163.0, 134.4, 129.7, 128.9, 127.6, 123.7, 114.2, 78.5, 55.5. Anal. Calcd for $C_{17}H_{13}NO_5$ (311.3): C 65.59; H 4.21; N 4.50. Found: C 65.48; H 4.16; N 4.49.

***N*-(2-Oxo-2-*p*-chlorophenylethoxy)phthalimide (3m).** White crystals from ethanol, yield (83%), mp 164-165 ºC. (Lit.[20] mp 162-163 ºC). LCMS: *m/z* = 318 (M + 3), 316 (M + 1). ^{1}H NMR ($CDCl_3$) δ 8.01 (dd, 2H, *J* 8.4, 1.6 Hz), 7.89-7.86 (m, 2H), 7.81-7.78 (m, 2H), 7.51 (dd, 2H, *J* 8.4, 1.6 Hz), 5.37 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 191.3, 163.0, 140.4, 134.5, 132.5, 129.4, 129.0, 128.5, 123.5, 78.4.

***N*-(2-Oxo-2-*p*-nitrophenylethoxy)phthalimide (3n).** Colorless crystals from ethanol, yield (88%), mp 180-82 ºC (Lit.[20] mp. 178-180 ºC). LCMS: *m/z* = 327 (M + 1). ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 2H, *J* 8.8 Hz), 8.28 (d, 2H, *J* 8.8 Hz), 7.90-7.886 (m, 2H), 7.83-7.79 (m, 2H), 5.41 (s, 2H). ^{13}C NMR ($DMSO_{d6}$) δ 192.3, 162.6, 150.2, 139.0, 134.9, 129.6, 128.6, 123.9, 123.3, 78.9.

Synthesis of compounds 7a-c. General procedure

To a mixture of compounds **3a,b,l** (10 mmol), phenylhydrazine (10 mmol) in ethanol (20 mL) was heated for 30 minutes and then ice water (50 mL) was added to the reaction mixture. The yellow precipitate so formed was then collected and crystallized from ethanol to give **7a-c**.

2-(2-Phenylhydrazinopropoxy)isoindole-1,3-dione (7a). Yellow crystals from ethanol, mp 135-136 ºC yield (70%). LCMS: *m/z* = 310 (M + 1). MS: *m/z* = 309 (M^+, 60%), 174 (45%), 161 (100%), 147 (70%). IR (KBr) 3334, 3052, 2915, 1726, 1601, 1494, 1369, 1242, 1123, 974, 876, 749, 695. ^{1}H NMR ($CDCl_3$) δ 7.79-7.76 (m, 2H), 7.71-7.67 (m, 2H), 7.25 (br, 1H), 7.13 (t, 2H, *J* 7.6 Hz), 6.89 (d, 2H, *J* 7.8 Hz), 6.79 (t, 1H, *J* 7.4 Hz), 4.76 (s, 2H, CH_2), 2.15 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$) δ 167.9, 142.5, 142.3, 134.4, 132.6, 129.1, 123.6, 123.0, 114.4, 68.9, 13.1. Anal. Calcd for $C_{17}H_{15}N_3O_3$ (309.3): C 66.01; H 4.89; N 13.58. Found: C 66.00; H 4.86; N 13.49.

2-(2-Phenyl-2-phenylhydrazinoethoxy)isoindole-1,3-dione (7b). Yellow crystals from ethanol, mp 165-166 ºC yield (78%). LCMS: *m/z* = 372 (M + 1). MS: *m/z* = 371 (M^+, 60%), 209 (75%), 103 (100%). IR (KBr) 3303, 3036, 1785, 1729, 1600, 1492, 1256, 1182, 1136, 974, 878, 754, 696. ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H, NH), 7.96-7.93 (m, 2H), 7.91-7.88 (m, 2H), 7.81 (d, 2H, *J* 8.4 Hz), 7.44 (t, 2H, *J* 8.0 Hz), 7.36-7.32 (m, 5H), 6.91-6.87 (m, 1H), 5.39 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 163.5, 144.7, 137.2, 135.2, 135.0, 129.2, 128.6, 127.8, 125.0, 123.5, 122.9, 120.3, 112.9, 69.2. Anal. Calcd for $C_{22}H_{17}N_3O_3$ (371.4): C 71.15; H 4.61; N 11.31. Found: C 71.08; H 4.46; N 11.29.

2-(2-*p*-Methoxyphenyl-2-phenylhydrazinoethoxy)isoindole-1,3-dione (7c). Yellow crystals from ethanol, mp 168-170 ºC yield (68%). LCMS: *m/z* = 402 (M + 1). MS: *m/z* = 401 (M^+, 60%), 174 (45%), 161 (100%), 147 (70%). IR (KBr) 3281, 3029, 2953, 1784, 1732, 1494, 1354, 1255, 1160, 977, 829, 698. ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H, NH), 7.97-7.94 (m, 2H), 7.92-7.89 (m, 2H), 7.76 (d, 2H, *J* 8.4 Hz), 7.33-7.30 (m, 4H) 7.01 (d, 2H, *J* 8.4 Hz), 6.89-6.86 (m, 1H), 5.35 (s, 2H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 163.9, 159.7, 145.4, 135.0, 135.5, 130.2, 129.7, 129.1, 127.0, 124.0, 120.5, 114.5, 113.3, 69.9, 55.7. Anal. Calcd for $C_{23}H_{19}N_3O_4$ (401.4): C 68.82; H 4.77; N 10.47. Found: C 68.78; H 4.76; N 10.39.

Product analysis

Flash vacuum pyrolysis

The apparatus used was similar to the one which has been described in our recent publication.[6] The sample was volatilized from a tube in a Buchi Kugelrohr oven through a 30 x 2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 500 ºC, the temperature being monitored by Pt/Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and pump. Under these condition the contact time in the hot zone was estimated to be =10 ms. The different zones of the product collected in the U-shaped trap were analyzed by ^{1}H, ^{13}C NMR, IR and GC-MS. Relative and percent yields were determined from NMR.

Pyrolysis products

2-Oxopropanal (5a). MS: *m/z* = 72 (M^+, 20%). ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1H), 2.44 (s, 3H, CH_3).[21]

Phenylglyoxal (5b). Mp 90-91 ºC (lit.[22] mp 90-91 ºC). ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1H), 8.21 (d, 2H, *J* 7.6 Hz), 7.66 (t, 1H, *J* 7.6 Hz), 7.52 (d, 2H, *J* 7.6 Hz).

3-Oxobutanal (5c). MS: *m/z* = 86 (M^+, 20%). ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 4.52 (s, 2H, CH_2), 2.32 (s, 3H, CH_3).[23]

Morpholino-4-yl-oxoacetaldehyde (5d). MS: *m/z* = 143 (M^+, 40%), 114 (100%). ^{1}H NMR ($CDCl_3$) δ 9.48 (s, 1H), 3.58-3.55 (m, 4H), 3.42-3.39 (m, 4H).[24]

***N,N*-Dimethylglyoxylamide (5e)**. MS: *m/z* = 101 (M^+, 30%), 45 (60%). ^{1}H NMR ($CDCl_3$) δ 9.51 (s, 1H), 3.20 (s, 3H, CH_3), 3.06 (s, 3H, CH_3).[25]

Ethyl glyoxalate (5f). LCMS: *m/z* = 102 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1H), 4.40 (q, 2H, *J* 6.8 Hz), 1.38 (t, 3H, *J* 6.8 Hz).[26]

Glyoxylonitrile (5g). MS: *m/z* = 55 (M^+, 80%). ^{1}H NMR ($CDCl_3$) δ 9.32 (s, 1H). IR (KBr) 2252 (CN), 1737 (CO).[27]

***p*-Methylbenzaldehyde (5h)**. ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 7.80 (d, 2H, *J* 8.0 Hz), 7.35 (d, 2H, *J* 8.0 Hz), 2.40 (s, 3H).[28a]

***p*-Cyanobenzaldehyde (5i).** ^{1}H NMR ($CDCl_3$) δ 10.12 (s, 1H), 8.02 (d, 2H, *J* 8.4 Hz), 7.87 (d, 2H, *J* 8.4 Hz).[29]

***p*-Chlorobenzaldehyde (5j).** ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 1H), 7.89 (d, 2H, *J* 8.4 Hz), 7.54 (d, 2H, *J* 8.4 Hz).[28b]

Benzaldehyde (5k). ^{1}H NMR ($CDCl_3$): δ 10.05 (s, 1H), 7.90 (d, 2H, *J* 7.6 Hz), 7.67 (t, 1H, *J* 7.4 Hz), 7.56 (t, 2H, *J* 7.5).[26c]

***p*-Methoxyphenylglyoxal (5l).** Yellow oil. LCMS: *m/z* = 165 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.67 (s, 1H), 8.23 (dd, 2H, *J* 8.4, 1.6 Hz), 6.97 (dd, 2H, *J* 8.4, 1.6 Hz), 3.78 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 190.2, 187.1, 167.4, 131.0, 129.2, 114.7, 55.9.[30]

***p*-Chlorophenylglyoxal (5m).** Mp 42-44 ºC (lit.[31] mp 40-41 ºC). LCMS: *m/z* = 171 (M + 3), 169 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1H), 8.31 (d, 2H, *J* 8.4 Hz), 8.16 (d, 2H, *J* 8.4 Hz). ^{13}C NMR (DMSO-d_6) δ 191.4, 189.3, 141.5, 131.3, 129.2, 129.1.

***p*-Nitrophenylglyoxal (5n)** Yellow oil. LCMS: *m/z* = 180 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1H), 8.39 (d, 2H, *J* 8.8 Hz), 8.06 (d, 2H, *J* 8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 191.4, 187.3, 154.5, 142.5, 130.6, 124.2.[30]

Phthalimide (6). Mp 232-234 ºC (lit.[32] mp 232-235 ºC). ^{1}H NMR (DMSO-d_6) δ 10.83 (s, 1H, NH), 7.90-7.87 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 167.9, 134.4, 132.6, 123.6.

2-Phenylhydrazonopropionaldehyde (9a). Mp.116-118 ºC (lit.[33] mp115-116 ºC). LCMS: *m/z* = 163 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.51 (s, 1H, CHO), 8.21 (br, 1H, NH), 7.37 (t, 2H, *J* 7.6 Hz), 7.30 (d, 2H, *J* 7.8 Hz), 7.07 (t, 1H, *J* 7.4 Hz), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 190.8, 134.4, 129.5, 123.6, 123.0, 114.4, 14.7.

Phenyl-(phenyhydrazono)acetaldhyde (9b). Mp. 113-115 ºC (lit.[33] mp. 115-116 ºC). LCMS: *m/z* = 225 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.47 (s, 1H, CHO), 8.45 (br, 1H, NH), 7.26 (d, 2H, *J* 7.8

Hz), 7.16 (t, 2H, *J* 7.6 Hz), 6.95 (t, 1H, *J* 7.6 Hz), 6.84 (d, 2H, *J* 7.8 Hz), 6.78 (t, 1H, *J* 7.7 Hz), 7.70 (t, 2H, *J* 7.6 Hz).

***p*-Methoxyphenyl-(phenylhydrazono)acetaldhyde (9c).** Yellow crystals, mp. 112-14 ^{o}C. LCMS: *m/z* = 255 (M + 1). ^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H, CHO), 7.49 (d, 2H, *J* 8.0 Hz), 7.16 (t, 2H, *J* 7.8 Hz), 7.15 (t, 1H, *J* 7.6 Hz), 6.85-6.83 (m, 4H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 193.2, 160.5, 142.3, 133.7, 131.6, 127.3, 125.9, 123.4, 112.9, 112.4, 53.2. Anal. Calcd for $C_{15}H_{14}N_2O_2$ (254.3): C 70.85; H 5.55; N 11.02. Found: C 70.78; H 5.46; N 11.00.

Acknowledgements

The support of Kuwait University received through research grant no. SC10/07 and the facilities of ANALAB/SAF (grants no. GS01/03, GS02/01, GS01/05) are gratefully acknowledged.

References

1. Repic, O. *Principles of Process Research and Chemical Development in the **P**harmaceutical Industry* John Wiley & Sons Inc.: New York, 1998.
2. Lee, S. *Process Development Fine Chemical from Grams to Kilograms* Oxford Univ. Press, Oxford, 2001, p 30.
3. Emsley, J.; Freeman, W. H. *J. Chem. Edu.* **1995**, *72*, A72.
4. Wells, G. *Handbook of Petrochemicals and Processes* Gower Publishing Company Ltd.: Gower House, England, 1991.
5. (a) Al-Awadi, N. A.; Kaul, K.; El-Dusouqui, O. M. E. *J. Phys. Org. Chem.* **2000**, *13*, 499. (b) Al-Awadi, N. A.; El-Dusouqui, O. M. E.; Kaul, K.; Dib, H. H. *Int. J. Chem. Kinet.* **2000**, *32*, 403. (c) Al-Awadi, N. A.; Elnagdi, M. H.; Kaul, K.; Illingovan, S.; El-Dusouqui, O. M. E. *Tetrahedron* **1998**, *54*, 4633. (d) Al-Awadi, N. A.; Elnagdi, M. H.; Kaul, K.; Illingovan, S.; El-Dusouqui, O. M. E. *J. Phys. Org. Chem.* **1999**, *12*, 654. (e) Al-Awadi, N. A.; Al-Bashir, R. F.; El-Dusouqui, O. M. E. *Tetrahedron Lett*. **1989**, *30*, 1699. (f) Shorter, J. *Pure & Appl. Chem*. **1994**, *66*, 2451.
6. (a) Al-Awadi, N. A.; Ibrahim, Y. A.; Patel, M.; George, B. J.; Al-Etaibi, A. M. *Int. J. Chem. Kinetic* **2007**, *39*, 59. (b) Ibrahim, Y. A.; Al-Awadi, N. A.; Ibrahim, M. R. *Tetrahedron* **2004**, *60*, 9121.
7. Dib, H. H.; Al-Awadi, N. A.; Ibrahim, Y. A.; El-Dusouqui, O. M. *J. Phys. Org. Chem*. **2004**, *17*, 267.
8. Al-Awadi, S.; Abdallah, M.; Hasan, M.; Al-Awadi, N. A. *Tetrahedron* **2004**, *60*, 3045.
9. (a) Dcrary, J. W.; Quayle, O. R.; Lester, C. T. *J. Am. Chem. Soc*. **1956**, *78*, 5584. (b) Jensen, K. A. *J. Prakt. Chem.*, **1938**, *151*, 167.
10. Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc*. **1953**, *75*, 2439 and references cited therein.

11. Buchalska, E.; Madura, I.; Okrasa, K.; Plenkiewicz, J.; Zachara, G. *Tetrahedron Asymm*. **2000**, *11*, 1781.
12. Consonni, P.; Favara, D.; Omodei-Sale, A.; Bartolini, G. and Ricci, A. *J. Chem. Soc. Perkin, Trans 2* **1983**, 667.
13. Ohto, N.; Tonomura, Y.; Sawaki, J.; Sato, N.; Akiko, H.; Ikuta, M.; Shimazaki, M. *Heterocycles* **1991**, *32*, 965.
14. Ken, K. M.; Kenneth, M.; Ngugen, N.; Nighi, V.; Cross, D. *J. Org. Chem.* **1981**, *46*, 5188.
15. Galons, H.; Fiet, J.; Combert-Farnoux, C.; Miocque, M.; Bram, G. *Mol. Cryst. Liq. Cryst.* **1988**, *161*, 521.
16. Kano, K.; Anselme, J. *Tetrahedron* **1992**, *48*, 10075.
17. Rhone-Poulenc **1964**, 640150. *Chem. Abst*. **1965**, *62*, 14586f.
18. Mckay, A. F.; Garmaise, D. L.; Paris, G. Y.; Gelblum, S. *Can. J. Chem*. **1960**, *38*, 343.
19. Bartovic, A.; Bernard, D.; Netchitailo, P. *J. Heterocyclic Chem.* **2000**, *37*, 827.
20. Wang, S.; Li, X.; Li, J. *Ultrasonics Sonochemistry* **2008**, *15*, 33.
21. Kark, G.; Williv, V.; Reinhard, G.; Hans-Joachim, G.; Jurgen, S.; Henning, H. *J. Org. Chem*. **1989**, *54*, 383.
22. Chaudhari, S.; Akamanchi, K. *Synthesis* **1999**, 760.
23. Jacek, T; Ewa, Z. *Pol. J. Chem*. **1981**, *55*, 79.
24. Liu, Q.; Perreault, S.; Rovs, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066.
25. Michael, P. T.; Polivina, J. F. G.; Anthony, D. P.; Stephen, M. B.; Stehen, B. B.; James, D. C.; Brian, J. D. *Bioorg. Med. Chem*. **2003**, *11*, 2695.
26. Bailey, P.; Smith, P.; Pedrson, F.; Clegg, W.; Rosair, G.; Teat, S. *Tetrahedron Lett*. **2002**, *43*, 1067.
27. Lewis-Bevan, W.; Gaston, R.; Tyrell, J.; Stork, W.; Salmon, G. *J. Am. Chem. Soc.* **1992**, *114*, 1933.
28. FT NMR, Aldrich Catalog (a) *II* 938C, (b) *II* 940B, (c) *II* 932B.
29. Boehme, H.; Sutoyo, P. *Tetrahedron Lett.* **1981**, *22*, 1671.
30. Bhella, S. S.; Elango, M.; S. Ishar, M. P. *Tetrahedron* **2009**, *65*, 240.
31. Reid, C. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2455.
32. FT- NMR, Aldrich Catalog, *II*, 1458A.
33. Severin, T. *Chem. Ber.* **1978**, *111*, 1564.