Morpholinolysis of Esters Analogous to Flutamide in 90% Methanol-water

Nada. M. Youssef[1], Shawky Elshazly[1,2], Ezzat. A. Hamed[1,2]

[1]Department of Chemistry, Faculty of Science, Beirut Arab University, Beirut, Lebanon.

[2]Department of Chemistry, Faculty of Science, Alexandria University,Ibrahimia 21321, P.O. Box 426, Alexandria, Egypt.

Correspondence: Nada. M. Youssef, Department of Chemistry, Faculty of Science, Beirut Arab University, Beirut, Lebanon. E-Mail: nadayoussefjnainati@hotmail.com

Abstract

The kinetics of the reaction of ester analogous to flutamide namely nitrophenyl acetate, butyrate and isobutryrate with morpholine in 90%Methanol-water is measured spectrophotometrically and show second order rate constants. The second order rate constants as well as activation parameters were calculated at 25-45°C. The mechanism of acyl-oxgen fission pass through stepwise mechanism and the position of slow step depends on the nature and position of substituent in the ester group as well as the chain structure of the non-leaving group. The second order rate constants, activation parameters and the correlation between log $k_{A(25)}$ versus log $k_{A(45)}$ can decide the position of the slow step.

Keywords: Flutamide analogous, acyl-oxygen fission, uncatalyzed reaction, stepwise mechanism, concerted mechanism, n-butyrate, isobutyrate, Morpholine, 90% Methanol-water.

1. Introduction

Esters have been studied extensively due to its important role in biological, chemical, environmental industrial processes and many natural molecules (Ibrahim, El-atawy, El-Sadany & Hamed, 2011)

Reactions of amines with carbonyl compounds have intensively been investigated due to importance in chemistry as well as in biological processes (Um, Lee. E-J., & Lee. J-P, 2002) and the reaction mechanism has been fairly well known (Lee. J-P, Yoon & Um, 1999).

The reaction mechanism for aminolysis of carboxylic esters has been suggested to proceed through an addition intermediate in which the rate determining-step (RDS) is dependent on the basicity of the leaving group and the nucleophilic amine (Um et al. 2002). Linear free energy relationship such as Brønsted or Hammett equation has been the most popular probe to investigate the reaction mechanism

(Bernasconi, 1986). Nonlinear Brønsted-type plot has often been observed for aminolysis of carboxylic esters with a good leaving group, and has been attributed to a change in the RDS of a stepwise mechanism upon changing the basicity of the leaving group or the nucleophilic amines (Um et al. 2002).

It has long been known that either the acyl-oxygen bond or aryl-oxygen bond of phenyl esters can be cleaved depending on: (i) the structure of the ester, (ii) the nature of reagent (iii) the basicity of the leaving group anion compared to that of the attacking nucleophile (iv) the nature of substituent in the aryl or the acyl group containing the ester (Ibrahim, El-atawy, El-Sadany & Hamed, 2013) and (v) the relative ''hardness'' and ''softness'' of the reaction site and reagent. Competition between the two electrophillic centers in the ester substrate is well documented for reactions of nitrophenylsulfonates, sulfates and phosphates with nucleophiles (Feuer, Patai, 1969 & Buncel et al., 1975 & Kirby, Jencks, 1965). On the other hand, most carboxylic esters undergo acyl-oxygen scission(Feuer et al., 1969 & Kirby et al., 1965) partial Ar-oxygen scission was also reported attributable to the strong activation of the 1-position (ipso) of the phenolic group by the nitro groups (Guanti et al., 1975).

As a continuation of our work in the field of nucleophilic aryl and acyl reactions, (Hamed, 1997 & 2011; Hamed, El-Bardan, Saad, Gohar & Hassan 1997; El-Hegazy, Abdel-Fattah, Hamed & Sharaf, 2000; Fathalla, Kassem &

Hamed, 2009; Khattab, Hamed, Albericio, El-Faham, 2010). We addressed kinetic studies of the leaving group ability of phenol containing one or two electron withdrawing groups. Morpholine (Mo) was selected as nucleophile because it possess a comparable pKa value to those reported for many amino acids.

We studied the mechanism for the reaction of the esters **1-9** (Figure1) with Mo in 90% methanol-water to examine (i) the mode of scission whether is the CO-O or/and Ar-O bond scission pathways, (ii) The effect of nitro group position on rate and mechanism, and (iii) The effect of introduction of trifluoromethyl group (-CF$_3$) in addition to the nitro group.
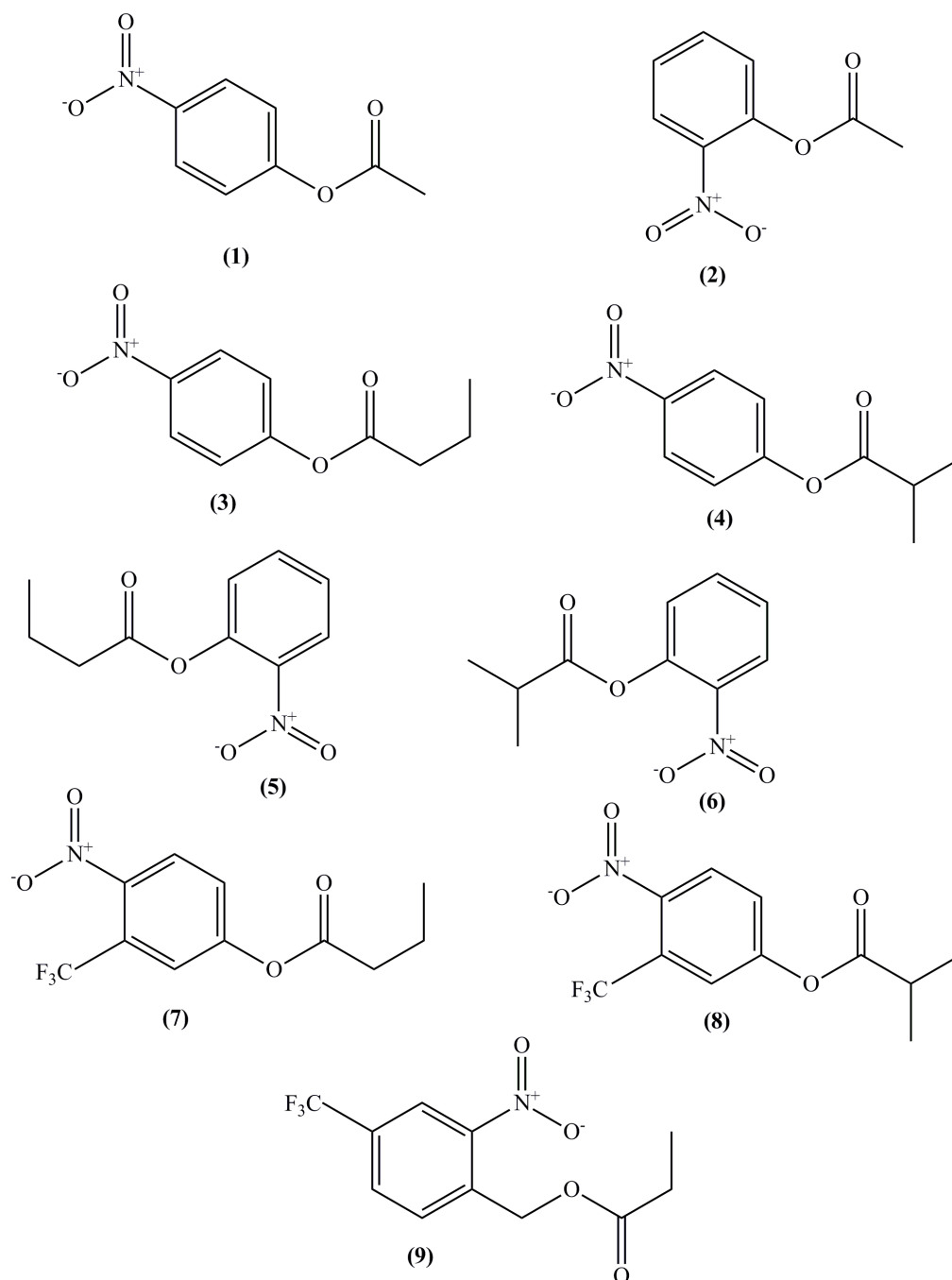

Figure 1. (Esters 1-9)

Ester (**8**) is analogues to flutamide (4-nitro-3-trifluoromethyl-isobutilanilide: Figure 2), but with an oxygen atom replacing nitrogen atom while the other esters differ from flutamide in the position of substitutent in the aromatic ring and the structure of the ester group –OR. Flutamide seems to have antiandrogenic specificity only in genitalia organs androgen-dependent, and its therapeutic use is in prostatic cancer (Brogden, Clissold, 1989).
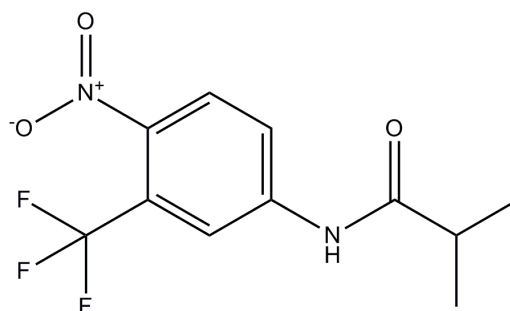
Figure 2. Flutamide

After human oral administration flutamide is quickly metabolized, producing about ten metabolites, mainly 2-hydroxyflutamide and 3-trifluoromethyl-4-nitroaniline Figures 3 & 4 (Jonler, Riehmann, Bruskewitz, 1994).
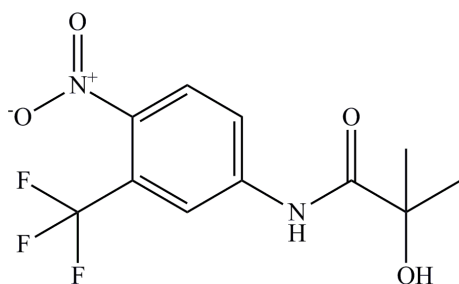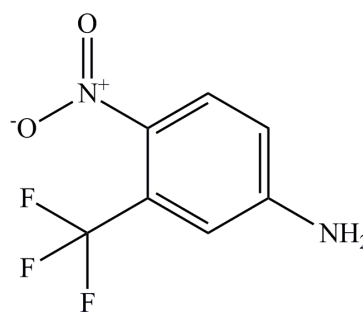

Figure 3. 2-hydroxyflutamide.

Figure 4. 4-Nitro-3-trifluoromethyl aniline.

2. Material and Methods

2.1 Materials

Methanol was obtained from Sigma Aldrich>99.99% and were used without further purification. Morpholine was obtained from Sigma Aldrich and used without distillation. The UV spectra were carried out on a V-730, UV-VIS spectrophotometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1600 series Fourier Transform instrument as KBr pellets. Nuclear Magnetic resonance spectra (^{1}H NMR spectra) were recorded on a JOEL 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard. Follow-up of the reactions and checks of the purity of the compounds was done by TLC on silica gel-protected aluminum sheets (Type 60 GF254, Merck) and the spots were detected by exposure to UV-lamp at λ = 254 nm for a few seconds.

2.2 Synthesis of the Starting Materials

2.2.1 Synthesis of 4-nitro-2-trifluoromethylphenol

A round bottom flask with a magnetic stirring bar was charged with 1-chloro-4-nitro-2- trifluoromethylbenzene (414mg, 2mmol) in ethanol. The reaction mixture was stirred with NaOH (1:2) for 1hour at room temperature, and then heated for 24 hours then allowed to cool to room temperature, diluted with 4-5mL of ethyl acetate and water, filtered and washed with 10-20mL of ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel (petroleum ether/ethylacetate1:1) to provide the desired product as a yellow solid (178 mg, Yield = 43%).

2.2.2 General Synthesis for the Preparation of esters (1-9)

Acid chlorides namely acetyl chloride, n-butyl chloride and isobutyl chloride (10mmol) were added to a mixture of phenols namely 2-nitrophenol, 4-nitrophenol, 4-nitro-3-trifluoromethyl phenol and 4-nitro-2-trifluoromethyl phenol, (10mmol) and Et₃N (2.8mL, 20mmol) in CH_2Cl_2 (5mL) as solvent. The reaction mixture was stirred for 3 hours at room temperature and then washed with saturated $NaHCO_3$ (2 × 10mL), saturated NaCl (2 × 10mL)

and H_2O ($2 \times 1mL$). The organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography (ethylacetate/hexane) as pale yellow liquids except for ester (**9**) which obtained as yellow solid. The spectral data of the prepared compounds are given below.

4-nitrophenyl n-butryrate (**3**): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1765 (C=O), 1524 (asym -NO_2), 1348 (sym-NO_2). ^{1}HNMR (CH$_3$OD) δppm :0.98-1.03 (H-4, 3H,t), 1.69-1.81 (H-3, 2H, m), 2.53-2.58 (H-2, 2H, t). ArH : 7.21-7.28 (H2',6', 2H, d), 8.17-8.22 (H3',5', 2H, d).

4-nitrophenyl isobutryrate (**4**): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1754 (C=O), 1530 (asym -NO_2), 1346 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm:1.58 (H-3, 6H, d), 3.25 (H-2, 1 H, m). ArH : 7.71-7.75 (H2',6', 2H, d), 8.66-8.69 (H3',5', 2H, d).

2-nitrophenyl n-butryrate (5): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1771 (C=O), 1532 (asym -NO_2), 1352 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm:0.98-1.06 (H-4, 3H,t), 1.66-1.78 (H-3, 2H, m), 2.55-2.6 (H-2, 2H, t). ArH : 7.25-7.28 (H-6', 1H, d), 7.38-7.44 (H-5', 1H, t), 7.65-7.71 (H-4', 1H, t), 8.03-8.05 (H-3', 1H, d).

2-nitrophenyl isobutryrate(6): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1768 (C=O), 1532 (asym -NO_2), 1352 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm:1.60-1.71 (H-3, 6H, d), 3.18-3.3 (H-2, 1 H, m). ArH : 7.66-7.67 (H-6', 1H, d), 7.83 (H-5', 1H, t), 8.10 (H-4', 1 H, t), 8.44-8.47 (H-3', 1 H, d).

4-nitro-3-trifluoromethylphenyl n-butryrate (**7**): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1772 (C=O), 1544 (asym -NO_2), 1358 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm: 1.038-1.31(H-4, 3H, t),1.74-1.87 (H-3, 2H, m), 2.62-2.64 (H-2, 2H,t). ArH : 7.491-7.528 (H-6', 1 H, dd, J = 2.4, 2.1 & 8.85Hz). 7.589-7.596 (H-2', 1H, s, J = 2.1 Hz), 7.972-8.001(H-5', 1 H, d, J = 8.7 Hz).

4-nitro-3-trifluoromethylphenyl isobutryrate (**8**): Pale yellow oil, IR (KBr,υ_{max}, cm^{-1}): 1769 (C=O), 1544 (asym -NO_2), 1358 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm:1.34-1.36 (H-3, 6H, d), 2.8-2.94 (H-2, 1 H, m). ArH : 7.484-7.521 (H-6', 1 H, dd, J = 2.4, 2.4 & 8.7 Hz).7.581-7.589 (H-2', 1H, d, J = 2.4Hz), 7.97-8.006 (H-5', 1H, d, J = 9Hz).

2-nitro-4-trifluoromethylphenyl n-butryrate (9): melting point = 68.5-70 ℃, IR (KBr,υ_{max}, cm^{-1}): 1780 (C=O), 1544 (asym -NO_2), 1348 (sym-NO_2). ^{1}HNMR (CD$_3$OD) δ ppm: 1.506-1.572 (H-4, 3H,m), 1.596-1.706 (H-3, 2H, m), 4.237-4.307 (H-2, 2H, t). ArH : 7.173-7.203 (H-6', 1H, d, J = 9Hz), 7.768-7.805 (H-5', 1H, dd, J = 2.4, 2.4, 9Hz), 8.117-8.123 (H-3',1H, dd, J = 1.8, 1.6, 10.5 Hz).

2.2.3 Kinetic Measurements

The kinetics of compounds (1 to 9) with morpholine was measured spectrophotometrically using a V-730 spectrophotometer. The kinetic runs were carried out at five temperatures (25 - 45°C) in 90% Methanol-water. The rates were measured spectrophotometrically by following the formation of aryloxide anions namely 2-nitrophenoxide at λ=410nm, 4-nitro-phenoxide at λ=400nm, 4-nitro-3-trifluoromethylphenoxide at λ=390nm and 2-nitro-4-trifluoromethylphenoxide at λ=395nm. All reactions were carried out under pseudo-first-order conditions, with various concentrations of morpholine (10^{-3} - 3×10^{-1}mol×dm^{-3}) and final concentration of esters used (10^{-4}mol×dm-3). The pseudo first-order rate constants k_{obs} were estimated by applying equation 1

$$\log(A_t - A_\infty) = \frac{-k_{obs} \times t}{2.303} + \log(A_0 - A_\infty)$$ (1)

Where A_0, A_t and A_∞ are the values of absorbance at zero time, time t, and at the end of the reaction, respectively. The A_∞ for each run was taken as the experimentally determined values, and k_{obs} is the pseudo-first-order rate constant.

3. Results and Discussion

3.1 Preparation of Starting Compounds 1 to 9

Reaction (1) of phenol derivatives (10-13) with acetyl, butyryl and isobutyryl chlorides afforded the rapid formation of esters (1 to 9) in good yields as a pale yellow oily products except for ester (9) which was obtained as yellow solid (Reaction 1).

The molecular structure of 4-nitrophenyl acetate (**1**) and 2-nitrophenyl acetate (**2**) is identified by IR. The IR spectrum of esters (**3-9**) show one sharp peak at wave number υ 1754-1780 cm^{-1} corresponding to the ester C=O group. The two peaks at υ 3286-1524-1544and 1346-1358 cm^{-1}are assigned to the asymmetric and symmetric stretching vibrations of the NO_2 group respectively (Socrates, 1980).
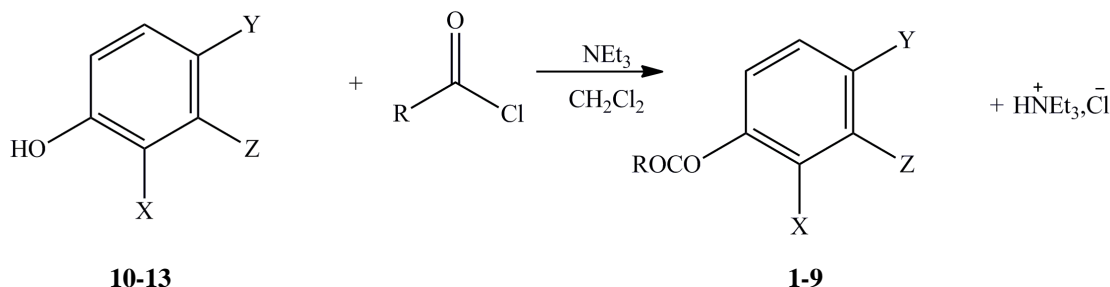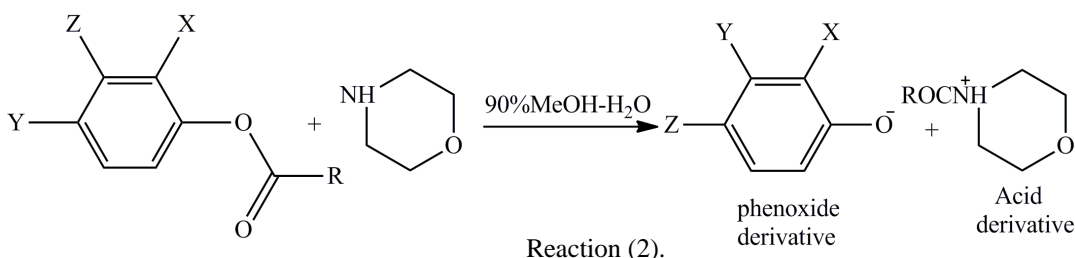
Reaction (1)

1. $X=Z=H$, $Y=NO_2$, $R= CH_3$
2. $X=NO_2$, $Y=Z=H$, $R= CH_3$
3. $X=Z=H$, $Y=NO_2$, $R= $ n-propyl
4. $X=Z=H$, $Y=NO_2$, $R= $ isopropyl
5. $X=NO_2$, $Y=Z=H$, $R= $ n-propyl
6. $X=NO_2$, $Y=Z=H$, $R= $ isopropyl
13. $X=NO_2$, $Y= CF_3$, $Z=H$

7. $X=H$, $Y=NO_2$, $Z= CF_3$, $R= $ n-propyl
8. $X=H$, $Y=NO_2$, $Z= CF_3$, $R= $ isopropyl
9. $X= NO_2$, $Y= CF_3$, $Z= H$, $R= $ n-propyl
10. $X=Z=H$, $Y=NO_2$
11. $X=NO_2$, $Y=Z=H$
12. $X=H$, $Y=NO_2$, $Z= CF_3$

The ^{1}H- NMR spectrum of **(3,5** and**7)** containing n-propyl group in CH$_3$OD show triplet peak at δ 0.98-1.31ppm representing CH$_3$ group, multiplet peak at δ 1.66-1.87 ppm corresponding to CH$_2$ group, triplet peak 2.53-2.64ppm corresponding to CH$_2$ group.The aromatic protons of these esters positioned in therange 7.2-8.0ppm depending on the position and nature of NO$_2$- and CF$_3$ substituents. Also, The ^{1}H NMR spectrum of **(4,6** and **8)** containing isopropyl group in CH$_3$OD show multiplet peak at δ 2.8-3.3ppm representing CH group and doublet peak at δ 1.34-1.7ppm corresponding to two methyl groups.

3.2 Reaction Products.

The mopholinolysis of substituted phenyl acetate, n-butyrate and isobutyrate **(1 to 9)** with morpholine in 90% Methanol-water mixed solvent proceeds exclusively through acyl-oxygen scission rather than aryl-oxygen scission as indicated from the identification of substituted phenoxide, reaction (2).

Reaction (2).

This is confirmed from the UV spectrophotometric matching of the known phenoxide derivatives with those obtained from reaction of compounds **(1 to 9)** with morpholine in 90% Methanol-water.

It was reported that the pka values of acetic (pka = 4.756, 4.800, n-butyric (pk$_a$ = 4.62, 4.83) and isobutyric acids (4.86, 4.84) are of lower values than 2-nitro (7.23, 7.57, 7.49), 4-nitro (pka = 7.15) and 4-nitro-3-trifluoromethyl phenols (pka = 6.0, 6.30) which means that the leaving group is the carboxylate ion. Actually, the observation of bands corresponding to aryloxide ions in the spectroscopic measurements indicates that the non-leaving group is –OCOR and the leaving group is the -OAr one although the latter have higher pka values. This is explained by the resonance between the lone pair on the oxygen of the ester group and 2-nitro and 4-nitro in compounds **(1 to 9)** which creates double bond character between this oxygen atom and the nitrophenyl ring. This directs the attack of morpholine on the carbonyl group followed by acyl-oxygen fission rather than aryl-oxygen fission.

3.3 Kinetic Study

3.3.1 Spectrophotometric Studies   .

The kinetic studies were performed spectrophotometricallyby monitoring the formation of nitrophenoxide anions between 390nm and 415nm for the reaction of **(1 to 9)** with morpholine. A representative full spectrum for the reaction of ester **(8)** with morpholine in 90% Methanol-water was measured spectrophotometrically by following the appearance of nitrophenoxide anions.
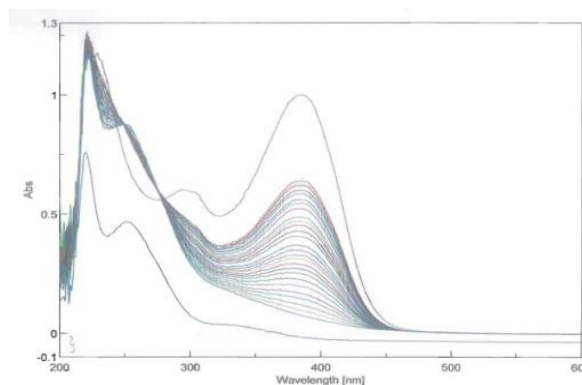
Figure 5. Full curve for the reaction of 4-nitro-3-trifluoromethyl phenyl isobutyrate (**8**) with morpholine in 90% Methanol-water at room temperature

3.3.2 Kinetics and Search for morpholine Catalysis.

The reactions of the esters (**1-9**) with morpholine obeyed pseudo-first-order rate constants (k_{obs}) which were obtained from the slope of the linear plot of $\ln(A_\infty-A_t)$ *vs.* time, Table.1. The linear plots of k_{obs} *vs.* amine concentration, indicated that no third-order terms were detected, and no complications were found in the determination of k_{obs}. This suggests that there is no base-catalysis and the contribution of H_2O or noticeable side reactions are negligible. Thus,   the over all reactions follows second order reaction. Second-order rate constants (k_A) were calculated from the slope of the linear plots of k_{obs} *vs.* amine concentrations. Similar values of k_A were obtained by dividing k_{obs} by the corresponding morpholine concentration, table.2. Therefore these reactions obey a clean second-order rate law, Equations 2 and 3.

$$\text{Rate} = k_{obs} \times [\text{Ester}] \tag{2}$$

$$k_{obs} = k_A \times [\text{Morpholine}] \tag{3}$$

Table 1. Search for morpholine Catalysis. First order rate constants k_{obs} and Second-order rate constants k_A in reaction of esters (1 to 9) with morpholine in 90% Methanol-water at 25°C.

$10^3\times$[Morpholine] in mol.l^{-1}	k_{obs}x10^5s^{-1}								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1.0	3.49	----	----	----	----	----	23.00	11.78	34.50
2.0	7.95	----	----	----	----	----	26.90	19.30	53.70
3.0	15.00	----	----	----	----	----	7.2.90	28.80	88.30
4.0	28.00	----	----	----	----	----	96.00	36.00	111.00
5.0	----	23.00	----	----	----	----	11.50	----	138.00
5.5	----	29.60	----	----	----	----	----	----	----
6.0	38.40	32.90	----	----	----	----	15.30	43.20	----
6.5	----	37.10	----	----	----	----	----	----	----
7.0	----	38.40	----	----	----	----	----	----	----
7.5	----	42.20	----	----	----	----	----	----	----
10.0	----	----	18.80	12.70	----	----	----	----	----
15.0	----	----	24.60	20.20	----	----	----	----	----
20.0	----	----	3.35	23.80	----	----	----	----	----
25.0	----	----	42.70	37.00	----	----	----	----	----
30.0	----	----	52.80	45.00	----	----	----	----	----
35.0	----	----	64.5	55.10	----	----	----	----	----
50.0	----	----	----	----		5.00	----	----	----
100.0	----	----	----	----	173.00	10.30	----	----	----
150.0	----	----	----	----	203.00	14.00	----	----	----
200.0	----	----	----	----	234.00	20.40	----	----	----
250.0	----	----	----	----	280.00	26.40	----	----	----
300.0	----	----	----	----	345.00	32.00	----	----	----
$10^2 k_A$ l. mol^{-1} s^{-1}	**8.10**	**7.20**	**1.84**	**1.70**	**0.800**	**0.110**	**26.00**	**6.40**	**26.40**

Table 2. The second order rate constants k_A (l.mol^{-1} s^{-1}) and activation parameter values for the morpholinolysis of compounds (**1 to 9**) in 90% Methanol-water at different temperatures (25-45°C).

| t$^{\circ}$C	$10^2 k_A$ l.mol^{-1}.s^{-1}								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
25	8.10	7.20	1.84	1.70	0.80	0.11	26.00	6.40	26.40
30	9.60	9.30	2.30	1.92	0.88	0.12	27.60	9.90	49.80
35	11.20	10.40	2.98	2.47	0.95	0.14	31.50	12.8	72.90
40	14.50	12.20	4.00	3.06	1.17	0.16	36.40	14.1	103.60
45	15.30	13.00	5.44	3.64	1.50	0.20	41.00	18.2	149.69
$\Delta H^{\#}$(kJ.mol^{-1})	24.17	20.47	40.71	29.03	26.75	21.54	16.31	8.57	63.78
$-\Delta S^{\#}$(J.mol^{-1}K^{-1})	184.91	197.52	142.20	181.69	200.95	229.98	201.83	234.44	40.70
$\Delta G^{\#}$(kJ.mol^{-1})	81.12	81.31	84.51	84.99	87.44	92.38	78.47	80.78	76.32
E_a(kJ.mol^{-1})	26.73	23.03	43.27	31.59	24.34	24.11	18.87	11.13	66.34

3.3.3 Reaction of Compounds (1 and 2) with Morpholine in 90% Methanol-water

It has been proposed that acyl-transfer reactions for esters and carbamates with nucleophiles proceed *via* either a *concerted, a stepwise* or a *substitution via elimination-addition* mechanism, depending on the nature of the nucleophile, the substrate, its leaving group and the solvents involved (Khattab, Hassan, Hamed, Albericio & El-Faham, 2010).

The values of $\Delta H^{\#}$ and $\Delta S^{\#}$ for the reaction of morpholine with esters (**1 & 2**) are respectively obtained from the Arrhenius plots. Table.2 shows low positive $\Delta H^{\#}$ and large negative $\Delta S^{\#}$ values indicating a rigid transition state or methanol molecules are greatly participate in the activated complex. This difference in rate constants as well as the $\Delta H^{\#}$ and $\Delta S^{\#}$ values are due to the degree of bond formation between the amine nucleophile and the carbonyl carbon. Shawali *et al*., (Shawali, Harhash, Hassanee, Alkaaabi, 1986) proposed a stepwise mechanism with rate limiting breakdown of a tetrahedral intermediate $T^{\pm}$ for the reaction of ester with amine. The stepwise mechanism (i) could involve two reaction pathways, an overall second-order, k_2, (uncatalyzed reaction), and an overall third-order, k_3 (the reaction is catalyzed by the amine) which is reject in our reaction. Alternatively, the morpholinolysis of esters (**1 & 2**) may proceed via a concerted mechanism involving transition state $T^{\pm}$concerted. (Castro, Aguayo, Bessolo, Santos, 2005).

The k_A values for the morpholinolysis of reactions of esters (**1 & 2**), with morpholine at temperatures 25-45°C are summarized in Table.2.

Our results could favor a concerted mechanism for the reaction of ester (**1**) with morpholine, (Scheme.1, pathway a), and a stepwise mechanism for the reaction of ester (**2**) with morpholine, (Scheme.1, pathway b). One can suggest $T^{\pm}$concerted for a concerted mechanism. Both the attack of the nucleophile and the departure of the leaving group are partially advanced. On the other hand, the reactions have been suggested to proceed through a zwitterionic tetrahedral intermediate with its formation or breakdown being the RDS (Um, Park, Fujio, Mishima, Tsuno, 2007). This suggestion might be consistent with observation that the rate constant of ester (**1**, 4-NO$_2$) is higher than ester (**2**, 2-NO$_2$) while the enthalpy of activation for the reaction of ester (**1**) is higher than this of ester (**2**). This can be used as an evidence for the different pathways of the nucleophillic acyl substitution (Um, Park , 2008). This previous concept is rejected because a $\Delta H^{\#}$ difference of 3.5 KJ/mole is hardly enough to unambiguouly favor one pathway. Also, entropy data is virtually ignored.
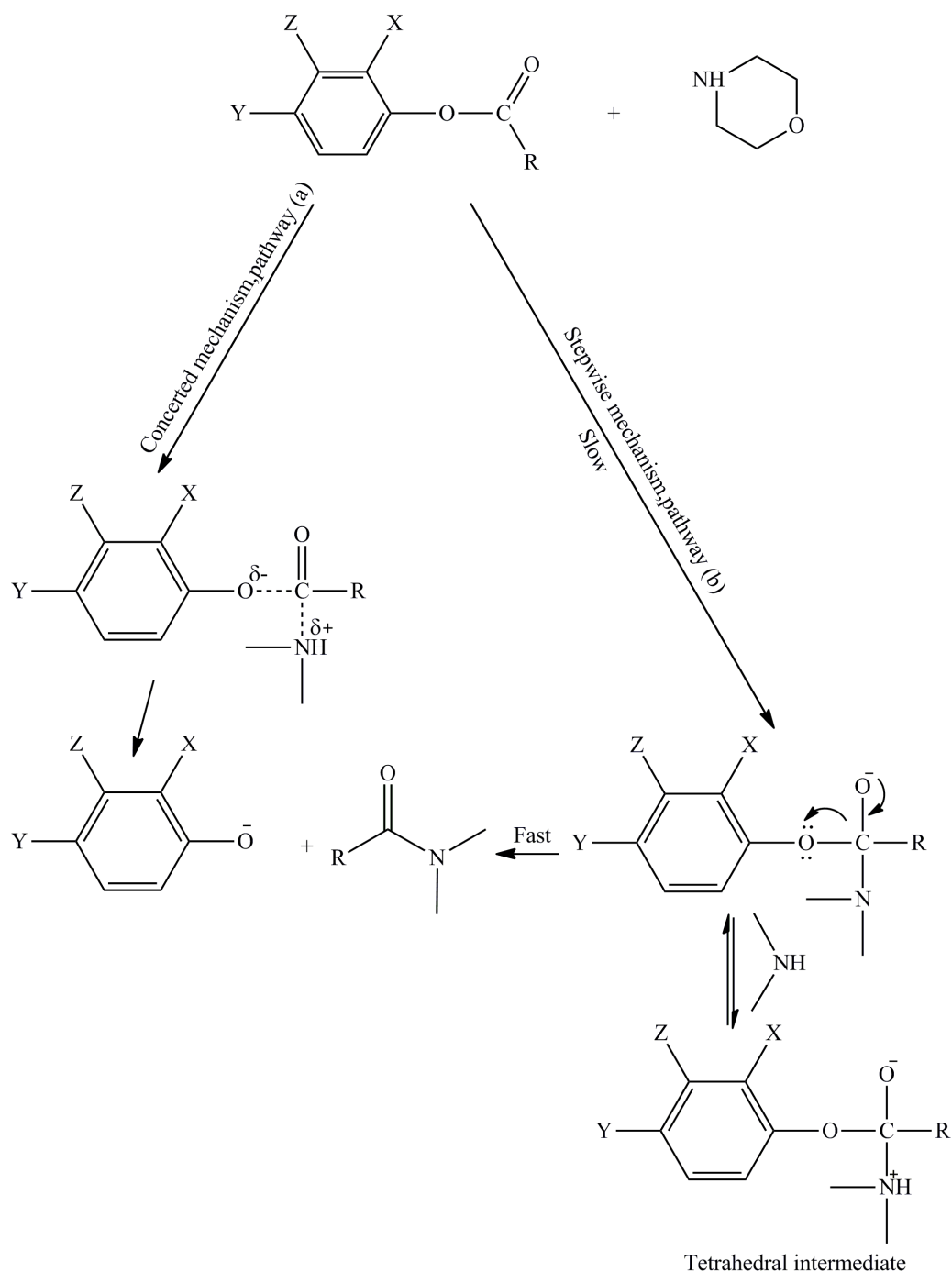
Accordingly, the previous results are possible when the reactions of esters **1** and **2** proceed through a *stepwise* mechanism with a change in the position of the rate-determining step, **Scheme.1**. The first step of the reaction is the addition of an N-H bond from Mo molecule to the carbonyl double bond in nitrophenyl acetate (**1 & 2**) and formation of a tetrahedral intermediate. This addition takes place through transition state TS1. The second step of the reaction is the conversion of the tetrahedral intermediate into morpholinolysis products through the transition state TS2.

TS1 **TS2**
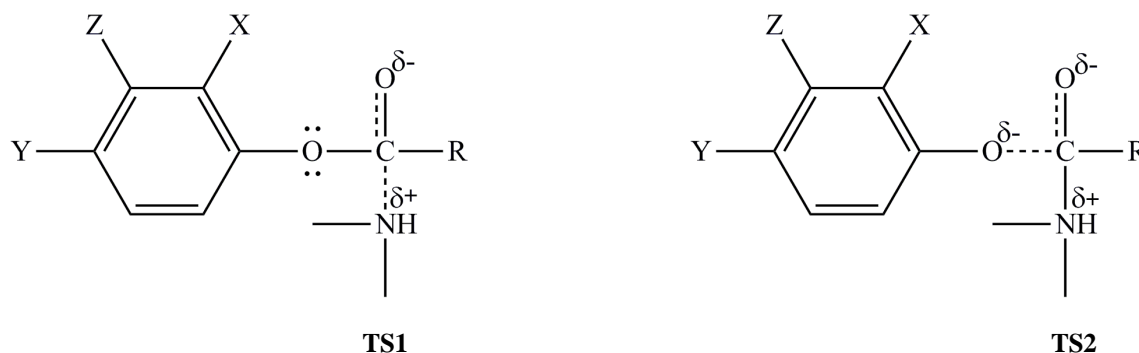
It was reported that the two transition states TS1 and TS2 have very similar energies and the nucleophilic attack is the rate determining step. A common feature of TS_1 and TS_2 is that departure of the leaving group is partially advanced, while the major structural difference between the two TS śs is the degree of bond formation between the amine nucleophile and the carbonyl carbon (*i.e.*, bond formation is advanced partially in TS_1 but fully in TS_2). Thus, one might suggest that TS_1 is less ordered than TS_2. This feature can be associated with different stabilities of nitrophenoxides as leaving groups as well as the structure of the non-leaving carboxylate group.

Table 2**:** Shows that

(i)   The reactions of esters (**3, 5, 7 and 9**) with n-propyl ester group and (**4, 6 and 8**) with isopropyl ester group and Mo are similar to the previously discussed for the reaction for esters (**1 & 2**) respectively. Esters with higher rate constants show higher enthalpy of activations and less negative entropy values.

(ii)   The second-order rate constants (k_A l.mol^{-1}s^{-1}) for the reactions of esters (**3 to 9**) with Mo increased with increasing temperature from 25 to 45°C.

(iii)   The reactivity of the esters (**1 to 9**) towards Mo increases as the basicity of the leaving group decrease i.e. rate constant ratio $k_A(7)/k_A(3)$ is 14.13-7.53 and $k_A(8)/k_A$ (4) is 3.23-1.21 as the pka of the conjugate base of the 4-nitro-3-trifluoromethyl phenoxide (**7**) increases from 6.0-6.3 (H_2O) to 7.15(H_2O) for 4-nitro-phenoxide at 25°C. Similarly, rate constant ratio of $k_A(5)/k_A$ (3)   is 2.3-3.62 for the reaction of Mo with (**3, 5**) as the pka increases from 6.0-6.3 for ester (**5**) to 7.23 and 7.15 l.mol$^-$ s^{-1} for ester (**3**). This is not attributed to the difference in acidity between parent acids: acetic acid, n-butyric acid and isobutyric acid because these acids have comparable pka values. Therefore, one can propose that the replacement of methyl by propyl or isopropyl in the non-leaving group and the pka of the leaving group influences the reactivity of the titled esters. In other words, the difference in the k_A between the two series of reactions is small due to the small difference between the leaving group basicity and when the leaving group basicity is the same, the reaction is from moderate to small dependent on the ester alkyl group except compounds (**7, 8**).

In general, the previous results are possible when the reactions of esters 1-9 proceed through a stepwise mechanism with a change in position of the rate-determining step, Scheme.1. The Arrhenius plots exhibit good linear correlations indicating that the activation parameters calculated from the slope and intercept are accurate, Table. 2 shows that the reaction of (**3, 5, 7**) results in approximately 11.68-5.21 kJ/mol lower $\Delta H^{\#}$ than that of (**4, 6, 8**) although (**3, 5, 7**) are more reactive than the corresponding esters (**4, 6, 8**) toward morpholine. However, this is expected on the basis of the structural difference between TS1 and TS2. One might expect that the energy released by formation of the C-N bond is smaller for the reaction of esters (**1, 3, 5, 7**) than for those of (**2, 4, 6, 8**) while the energy required to break the C-OAr bond in the TS2 is the opposite. This presumably accounts for the fact that the former reaction exhibits larger $\Delta H^{\#}$ than the latter reaction.

It is also noted that the reactions of esters (**2, 4, 6, 8**) exhibit 9.63-32.61 J.mol$^.$K^{-1} less negative $\Delta S^{\#}$ than those of (**1, 3, 5, 7**) indicating that TS1 is less ordered than TS2. Thus, one can consider TS1 as the TS structure for the reaction of (**1, 3, 5, 7**) and TS2 as the TS structure for the reactions (**2, 4, 6, 8**).

It is found that the plot of log k_A(25°C) versus log k_A(45°C) for the reactions of esters (**1-9**) with morpholine gives scattered point with r = 0.68 i.e. poor correlation, while such plot for the same reaction of series (**1, 3, 5, 7**) and (**2, 4, 6, 8**) gave good correlations. Similarly, the plot of $\Delta H^{\#}$ versus $\Delta S^{\#}$ for each series improves the correlation (r = 0.934) in contrast to the scattered points when all esters are used in the correlation. These observations are in agreement with the suggested stepwise mechanism with the transition states TS1 and TS2 for esters (**1, 3, 5, 7**) and esters (**2, 4, 6, 8**) respectively.

The relatively higher k_A values for the reaction of ester (**9**) with Mo than for ester (**7**) that contains the same

substituents $-CF_3$ and $-NO_2$ as   ester (9) but in different positions is presumably due to the $-CF_3$ substituent in ester (7). The 3-CF_3 substituent   slightly inhibits the effect of 4-NO_2 to stabilize the phenoxide anion leaving group, while kinetic data indicated that this steric effect is diminished in ester (9) that contains 2-CF_3 substituent..

Table. 2, reveals that k_A for esters (7, 9) which contain n-propyl ester group are larger than that of esters (8) which contains isopropyl ester group. This is due to the crowding affect of isopropyl group on their transition states. The comparison between the k_A values for the isopropyl ester (8) which contains $-CF_3$ and $-NO_2$ and the isopropyl ester (4) containing only 4-NO_2 group shows that the former is greater than the latter by approximately 5.16-3.23 times. This may be due to the presence of the electron withdrawing group $-CF_3$ which increases the electrophillicity of the carbonyl carbon reaction center.

4. Conclusion

The rate constants of the reaction of esters (1-9) with Mo, activation parameters and the correlation between log $k_{A(25)}$ versus log $k_{A(45)}$ indicates that esters follow stepwise mechanism with change in the position of the slow step. It was concluded that esters (1, 3, 5, 7) undergo slow attack of Mo to form tetrahedral intermediate via TS1 while esters (2, 4, 6, 8) passes through stepwise process in which the deprature of the leaving group via TS2 is the controlling step. Also, the presence of -CF_3 substituent in ester (7) inhibit the effect of 4-NO_2 to stabilize the phenoxide anion leaving group. Kinetic data indicated the steric effect is diminished for the reaction of ester (9) and the bulkness of isopropyl group leads to lower k_A values.

Future studies will be made to substantiate the mechanism such as (i) the use of more substrates with different electron withdrawing group and electron donating groups at different positions. (ii) apply computational quantum chemistry in studying the mechanism of morphinolysis of the titled esters.

References

Bernasconi, C. F. (1986). *Techniques of Organic Chemistry* (4th ed.). Wiley: New York, *6*.

Brogden, R. N., & Clissold, S. P. (1989). *Drugs*, *38*, 185. http://dx.doi.org/10.2165/00003495-198938020-00003

Buncel, E., Chuaqui, C., Forsythe, P., Mahoney, S., Raoult, A., & Willtshir, J. F. Perkin II. (1975). *J. Chem. Soc*, 478.

Castro, E. A., Aguayo, R., Bessolo, J., & Santos, J. G. (2005). *J. Org. Chem, 70*, 7788. http://dx.doi.org/10.1021/jo051052f

El-Hegazy, F. M., Abdel-Fattah, S. Z., Hamed, E. A., & Sharaf, S. M. (2000). *J. Phys. Org. Chem, 13*, 549. http://dx.doi.org/10.1002/1099-1395(200009)13:9<549::AID-POC297>3.0.CO;2-5

Fathalla, M. F., Kassem, T. S., & Hamed, E. A. (2009). *Indian J. Chem*, Sect, 47A, 1348.

Feuer, H., & Patai, S. (Eds.). (1969). *The Chemistry of the Nitro and Nitroso Groups,* Wiley-Inter science, New York.

Guanti, G., Dell'Erba, C., & Pero, F. (1975). *Chem. Commun*, *55,* 823. http://dx.doi.org/10.1039/c39750000823

Guanti, G., Dell'Erba, Pero, F., & Leandri, G. (1977). *J. Chem. Soc*, Perkin II. 966. http://dx.doi.org/10.1039/p29770000966

Hamed, E. A. (1997). *Int. J. Chem. Kinet, 29*, 599. http://dx.doi.org/10.1002/(SICI)1097-4601(1997)29:8<599::AID-KIN5>3.0.CO;2-P

Hamed, E. A. (2011). *Int. J. Chem. Kinet, 29*, 515. http://dx.doi.org/10.1002/(SICI)1097-4601(1997)29:7<515::AID-KIN5>3.0.CO;2-X

Hamed, E. A., El-Bardan, A. A., Saad, G. A., Gohar, G. A., & Hassan, G. M. (1997). *J. Chem. Soc., Perkin Trans, 2,* 2415. http://dx.doi.org/10.1039/a701902e

Ibrahim, M. F., El-atawy, M. A., El-Sadany, S. K., & Hamed, E. A. (2011). *Journal of Molecular Structure*, *1006*, 303–311. http://dx.doi.org/10.1016/j.molstruc.2011.09.024

Ibrahim, M. F., El-atawy, M. A., El-Sadany, S. K., Hamed, E. A. (2013). *Int. J. Chem. Kinet, 45*, 551–559. http://dx.doi.org/10.1002/kin.20779

Jonler, M., Riehmann, M., & Bruskewitz, R.C. (1994).*"Drugs"*, 47, 66. http://dx.doi.org/10.2165/00003495-199447010-00005

Khattab, N. S., Hassan, Y. S., Hamed, A. E., Albericio, F., & El-Faham, A. (2010). *Bull. Korean Chem.* Soc,

31(1), 75. http://dx.doi.org/10.5012/bkcs.2010.31.01.075

Khattab, S. N., Hassan, S. Y., Hamed, E. A., Albericio. F., & El-Faham, A. (2010). *Bull. Korean Chem. Soc.*

Kirby, A. J., & Jencks, W P. (1965). *J. Am. Chem. Soc*, *87*, 3209. http://dx.doi.org/10.1021/ja01092a036

Kirkien-Konasiewicz, A., & Maccoll, A. (1964). *J. Chem. Soc*, 1267-1274. http://dx.doi.org/10.1039/jr9640001267

Kirsch, J. F., & Clewell, W. A., & Simon, A. (1968). *J. Org. Chem*, *33*, 127. http://dx.doi.org/10.1021/jo01265a023

Lee, Jong-Pal., Yoon, Ji-Hui & Um, Ik-Hwan. (1999). *Bull. Korean Chem. Soc*, *20*, 7.

Menger, F. M., & Glass, L. E. (1974). *J. Org. Chem*, *39*, 2469-2470. http://dx.doi.org/10.1021/jo00930a052

Shawali, A. S., Harhash, A., Hassanee, H. M., & Alkaaabi, S. S. (1986). *J. Org. Chem, 51,* 3498. http://dx.doi.org/10.1021/jo00368a020

Socrates, G. (1980). *Infrared Characteristic Group Frequencies* , John Wiley & Sons.

Um, I. H., & Park Y. M. (2008). *Bull. Korean Chem. Soc*, *29*(3), 575. http://dx.doi.org/10.5012/bkcs.2008.29.3.575

Um, I. H., Min, J. S., Ahn, J. A., & Hahn, H. J. (2000). *J. Org. Chem*, *65,* 5659. http://dx.doi.org/10.1021/jo000482x

Um, I. H., Park, Y. M., Fujio, M., Mishima, M., & Tsuno, Y. (2007). *J. Org. Chem*, *72*, 4816. http://dx.doi.org/10.1021/jo0705061

Um, Ik-Hwan., Lee, Eun-Ju., & Lee, & Jong-Pal. (2002). *Bull. Korean Chem. Soc*, *23*(3), 381. http://dx.doi.org/10.5012/bkcs.2002.23.3.381

Copyrights