Kingdom of Saudi Arabia
Ministry of Higher Education
King Faisal University
Deanship of Scientific Research

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك فيصل
عمادة البحث العلمي

التقرير النهائى لبحث علمي

رقم ٤٠٠٦

تخليق بعض مركبات حمض الهيدروكساميك ذات الأهمية الطبية و البيولوجية

Synthesis of some biologically important hydroxamic acid derivatives

اعداد
د/يا سر بن سليمان بن صالح الفايز
أستاذ الكيمياء العضويه المساعد
بجامعة الملك فيصل

Synthesis of some biologically important hydroxamic acid derivatives

ملخص البحث(ABSTRACT)

في هذا البحث تم تشيد مجموعه من مشتقات حمض الهيدروكساميك *N*-alkyl-*O*-acyl hydroxamic acid النشطه وغير النشطه كذلك تم دراسة تفاعلات اعادة التنظيم لهذه المشتقات تحت تأثير القاعدي للأمين ثلاثي الأيثل حيث تعطي عملية إعادة التنظيم تلك طريقه جديدة لتخليق العديد من المركبات من المحتمل ان تكون هامه صناعيا وبيولوجيا وقد وجد ان هذه المركبات تتأثر بنوعية التغير الذي يتم في تركيبها.

واظهرت دراسة حركية هذا التفاعل احتمالية اتباعه لميكانيكية تفاعل من نوع اعادة تنظيم ٣،٣- سيجماتروبك.

1 Introduction

The hydroxamic acids are widely distributed in the nature and their characteristic structural elements have been found in several naturally occurring compounds. They have many magnificent roles in medicine and biology. Several naturally occurring hydroxamic acids have been isolated and many medicinally active derivatives have been synthesised.[1-7]

In next section we will review their biological activities in brief.

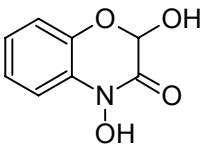
2 Some of Biological properties of hydroxamic acids

The hydroxamic acids have many magnificent roles in medicine and biology. Several naturally occurring hydroxamic acids have been isolated and many medicinally active derivatives have been synthesised.[1-7] In fact, they exhibit a wide spectrum of biological properties including selective enzymes inhibitors[1], anti-cancer agents,[2] siderophores,[3] and anti-fungal agents.[4]

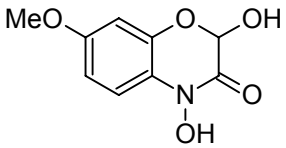
1.2 Chemical defence

Hydroxamic acids are found to be secondary metabolites of a wide spectrum of *Graminea,* such as wheat and maize. DIBOA (2,4-dihydroxy-1,4-benzoxazin-3-one) and DIMBOA

(2,4-dihydroxy-7-methoxy-1,4- benzoxazin-3-one) are cyclic hydroxamic acids which have been reported to play an important role in plants natural resistance to diseases and insects. In the plant these hydroxamic acids exist as glucosides that, upon injury to the plant tissue, are transformed to the toxic aglycones.[5]



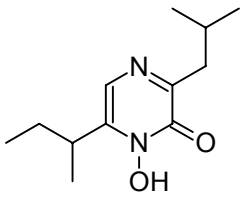
DIBOA



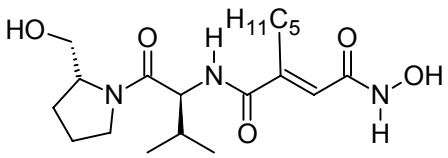
DIMBOA

1.۳ Antibiotics

Several natural antibiotic hydroxamic acids have been isolated and synthesised. Notable among these the heteroaromatic antibiotic aspergillic acid **1**,[6] and *N*-unsubstituted hydroxamic acid actinonin **2**.[7]



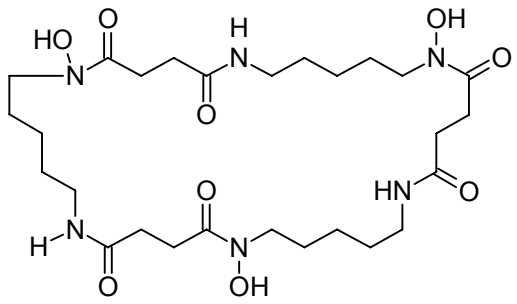
1



2

1.4 Siderophores

Siderophores are naturally occurring hydroxamic acids produced by many microorganisms, plants, fungi, and algae to transport iron (F^{3+}) from the outside environment into their cells.[8] Many of these hydroxamic acids have been isolated and synthesised, for example, DFOE (Nocardamine) **3** has been isolated along with eight other hydroxamic acid siderophores.[9]

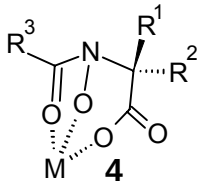


3

Investigations have shown that many microbes produce excess of siderophores when cultured in iron-deficient environment in attempt to take up more (F^{3+}).[10] Transformation of iron (F^{3+}) is essential for the proper function of enzymes that are responsible for electron and oxygen transportation in these cells.[11] This unique phenomenon has been widely employ in medicine. For example, they have been used for the diagnoses of bacterial infections,[12] and the treatment of the iron overload syndromes and toxic metals.[13]

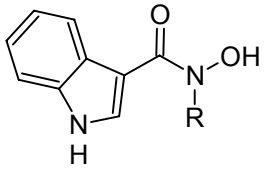
1.0 Enzymes inhibitors

The ability of hydroxamic acids to form strong metal complexes **4** with transition metals has been employed in use of hydroxamic acids as inhibitors of several metalloenzymes.[14]

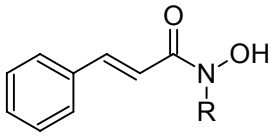


4

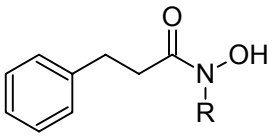
The activities of hydroxamic acids as inhibitors of the zinc-containing enzymes are well documented.[14-16] Summers *et al* have examined the effect of more than 100 hydroxamic acids on the activity of the 5-lipoxygenase enzyme (5-LO).[16] Since, the (5-LO) enzyme is associated with several diseases such as asthma, allergy, arthritis, and psoriasis the inhibition of this enzyme represents a potential new therapy.[16] The inhibitory potency of the hydroxamic acids tested were structure dependant. For example, the most effective inhibitors were of type **5**, when there is no spacer unit between the aromatic group and the hydroxamate group. Hydroxamic acids of type **6** were less potent while those with saturated spacer units as in **7** and **8**, reduced the hydroxamic acids inhibitory potency to their lowest level.[16] However, when the hydroxamate group has been replaced with other related functional groups no or little potency has been observed.[15]



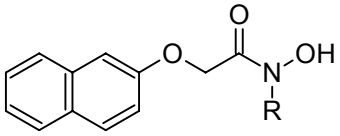
5



6

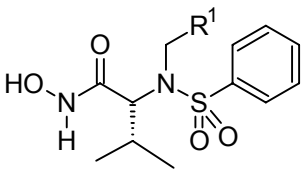


7

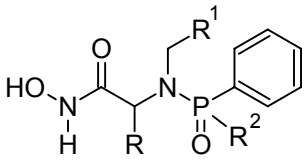


8

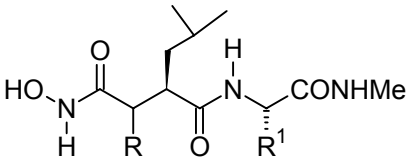
In a similar manner, the inhibitions of matrix metalloproteases (MMPs) enzymes have reported. Investigations show that hydroxamic acids of type **9**, **10** and **11** inhibit the enzymes while **12** do not.[17-18]



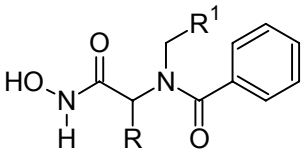
9



10



11

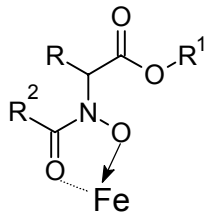


12

These compounds are in clinical tries for the treatment of human cancers, and tumour growth,[19] and arthritis.[18]

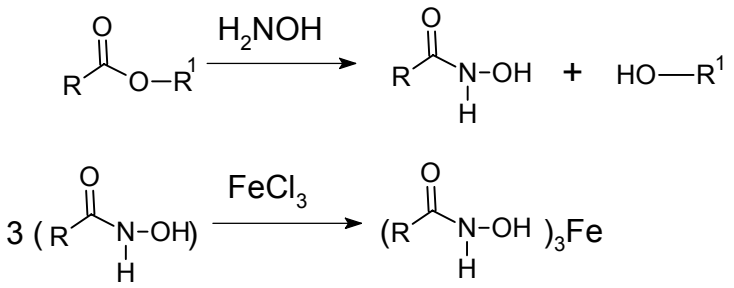
1.٦ Hydroxamic acids in analytical chemistry

We have already stated that hydroxamic acids can form metal complexes with a wide range of metals.[19] The kind of complexation has been used in the analytical chemistry as a classification test of the carboxylic acids and their derivatives.



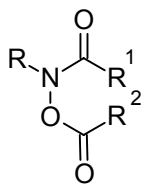
13

Hence, the presence carboxylic acids and their derivatives in unknown sample can be demonstrated by a reaction with hydroxylamine to yield hydroxamic acid. The addition of drops of ferric chloride to the solution produces the ferric hydroxamate complex, which has a characteristic burgundy or magenta colour, (Scheme 1).[20]



Scheme 1

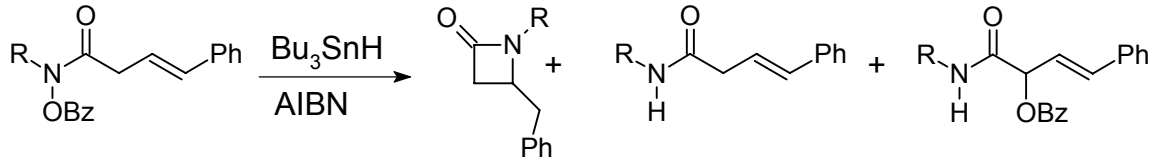
2 Chemistry of *N*-alkyl-*O*-acyl hydroxamic acids 14



14

.2.1 The discovery of the reaction

During cyclisation studies of *N*-alkyl-*O*-acyl hydroxamic acid derivatives a trace a mounts of 2-benzoyloxy amides as by-products were detected. For example, reaction of hydroxamic acid derivative **15** with Bu_3SnH-AIBN in refluxing toluene furnished not only the expected cyclisation **16** and reduction **17** product products but also 2-benzoyloxyamide **18** in 20 %, (Scheme 2).[21]

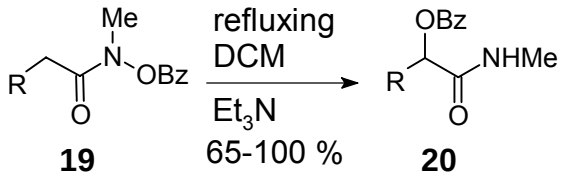


15 **16** **17** **18**

Scheme 2

Interestingly, a noticeable improvement in yield of the rearranged product **18** occurred when tristrimethylsilyl silane was the hydrogen donor. The rearrangements of hydroxamic acid derivatives of type **15** have also been to observe to occur under basic conditions in the absence of radical initiator (*e.g.* Et_3N or BTPP [tert-butylimino-tri (pyrrolidino) phosphorane]).[22]

Generally, *N*-alkyl-*O*-acyl hydroxamic acid derivatives of the type **20** undergo thermal and base catalysed rearrangement to give 2-benzoyloxy amides **21** in good to excellent yields (65-100 %), (Scheme 3).[21-22]



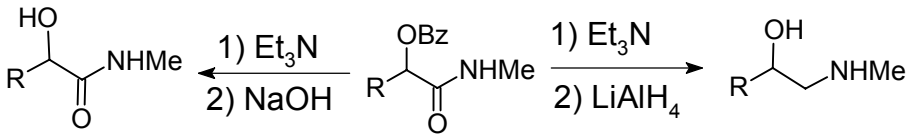
19 **20**

Scheme 3

2.2 The importance of this rearrangement

The product **20** represent suitably protected versions of 2-hydroxyamides a common feature in many natural products and many of their biological activity have been documented.[23] From the point view of organic synthesis, 2-hydroxyamides are versatile synthetic intermediates and con be utilized as building block to prepare peptide mimics,[22] precursors to ethanolamines,[24] oxindoles,[25] or oxazolidinediones.[26]

In recent studies has demonstrated that these rearranged compounds are useful precursors to 2-hydroxyamides, which can be obtained after deprotection of the hydroxyl group. Additionally, reduction furnishes important class of the amino alcohols, (Scheme 4).[23]

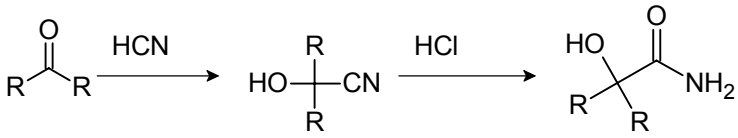


Scheme 4

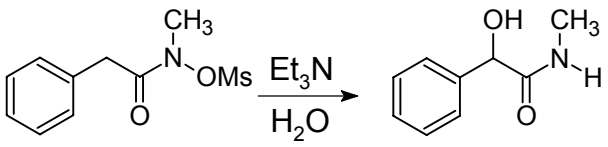
2.3 Method for the preparation of 2-hydroxy amides

In this section will briefly review the different methods currently available to furnish 2-hydroxyamides. Surprisingly, there are few methods to prepare 2-hydroxyamides. Many of these approaches depend upon reactions of electrophiles with organometallic reagents.

The most successful are the modification of Passerini reaction in which a Lewise acid is used as catalyst in the coupling reaction between isocyanides and aldehydes, (Scheme 5)[27] and the base promoted reaction of *O*-sulfonated hydroxamic acids derivatives in water, (Scheme 6).[28]



Scheme 5



Scheme 6

While the first procedure often suffers from low yields and uses highly toxic isocyanides the latter procedure is also not ideal because of the necessity of slow addition of the water to the reaction medium.

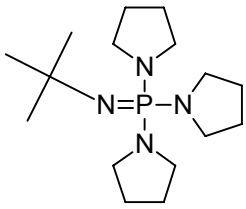
3 Previous work

A brief summary of the effect of the reaction conditions and substituents upon the rearrangement obtained from the previous studies.

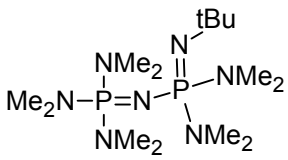
3.1 The reaction conditions

Many different bases were screened for their activity in mediating the rearrangement. Bases ranging from simple organic bases (such as Hunigs base, pyridine, Et_3N, and BTPP to stronger metallic bases such as LiHMDS, and KHMDS) were screened. The effects of different solvents and temperature were also investigated. However, it was found that using a catalytic amount Et_3N in refluxing toluene at 110°C was the most efficient conditions to facilitate the reactions.[22]

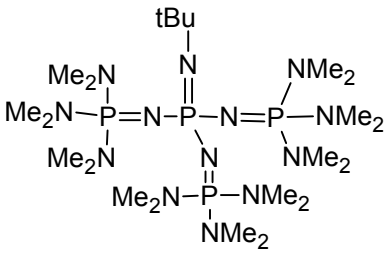
A variety of phosphazene bases have been used to facilitate the rearrangement of unactivated *N*-alkyl-*O*-benzoyl hydroxamic acid derivatives to 2-benzoyloxyamides. The rearrangement occurs smoothly in (6-100 %) yields *via* treatment with super phosphazene bases **21**, **22**, and **23** in dry toluene at 120°C.[22] However, the use of a catalytic (0. 2 eq) amount of P_2-^{t}Bu **23** is the most efficient method. [22]



21



22

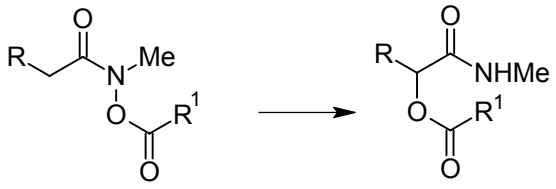


23

3.2 Effects of substituents

A range of different substrates were investigated, and the effect of the *O*-acyl substituents was examined. Benzoyl, acetyl, and pivaloyl, were all shown to be compatible with the

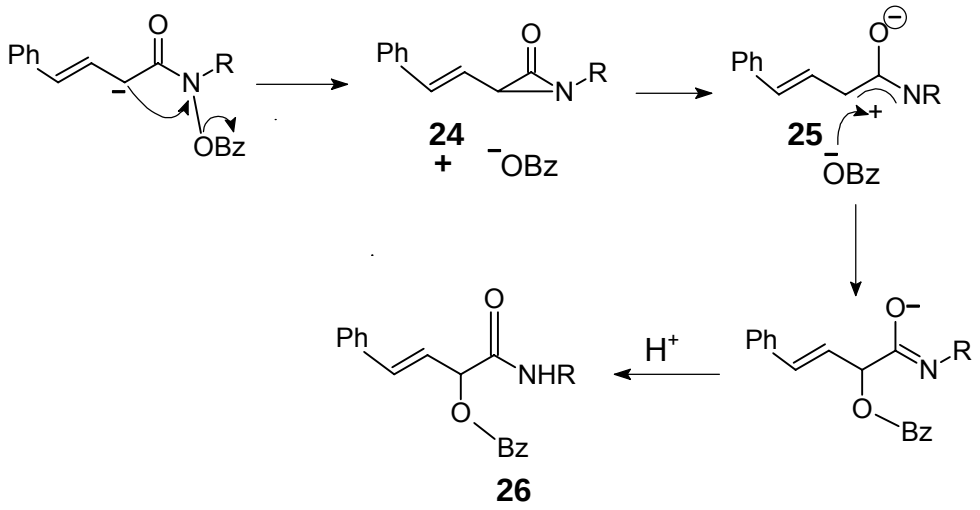
reaction conditions, (Scheme 7). However when benzoyl group was replaced the with electron withdrawing 4-nitrobenzoyl group markedly a increased rate and yield of the reaction was observed. It was concluded that the 4-nitrobenzoyl was a better leaving group[21-22]



Scheme 7

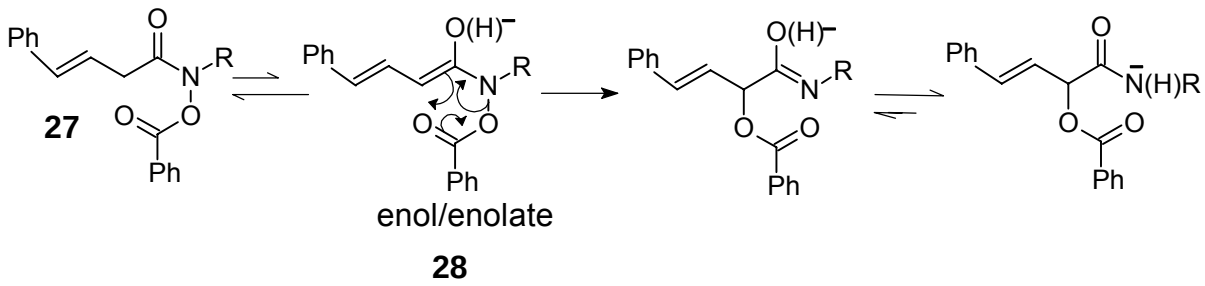
3.3 Possible mechanisms of the rearrangement reaction

Tow mechanisms were postulated for the reaction. The first mechanism involves formation of an enol or an enolate followed by nucleophilic displacement of the benzoyloxy group to furnish an α-lactam (**24**). After ring opening the α-lactam is trapped *via* the displaced anion (**25**) (which in this example is the benzyloxy anion) to give the rearranged product. (Scheme 8).[29-31]



Scheme 8

Alternatively, the rearrangement of benzoyl derived hydroxamic acid **27** could arise from a novel [3,3]-sigmatropic rearrangement of the enol or the enolate form of the derived **28**, (Scheme 9).[31]

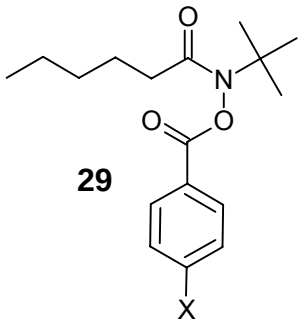


Scheme 9

4 Aims of this project

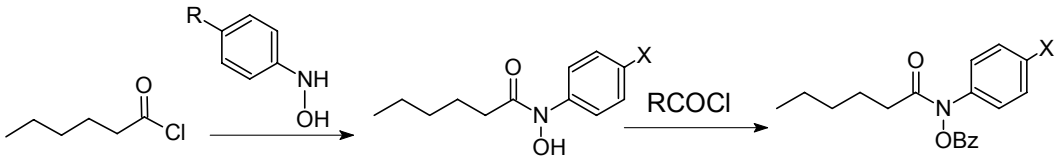
In the light of the previous results, our efforts will focus on the investigation of this rearrangement in more detail in particular to determine which, if any other types of precursors would undergo the rearrangement. We also wanted to determine in more detail the electronic effect of the *O*-acyl substituent upon the rearrangement.

We will look at different *O*-benzoyl group substituents **29** *eg* (X = Me, MeO, Cl) to study their electronic effects upon the reaction and to get more mechanistic information.



29

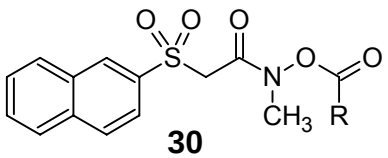
In addition the electronic effects of *N*-phenyl substituents *e.g.* (X = NO_2, Me etc) could be providing useful kinetic information, (Scheme 13).



Scheme 10

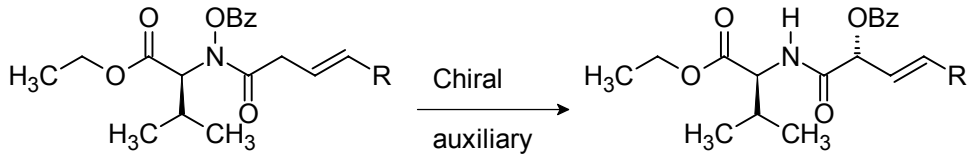
Accurate kinetic measurement and analysis using Hammett parameters would allow ρ value for the transformation to be determined which in turn might shed light into the mechanism of the process.

Further work could look at different *N*-activating groups, which may have a role in drug synthesis (e.g. (**30**)).



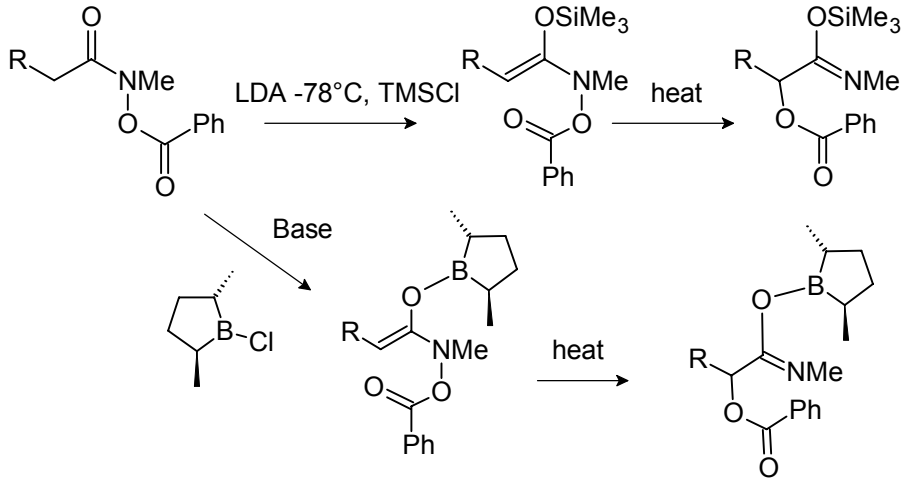
30

In order to develop an asymmetric variant of the reaction it may be possible to use chiral auxiliaries based upon amino acids, (Scheme 14) or to use chiral bases**.**



Scheme 11

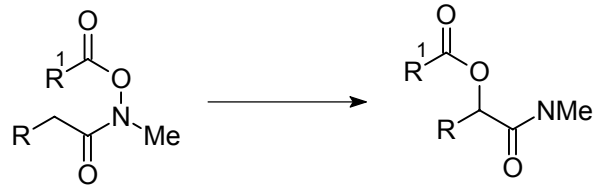
In order to utilise this approach it will be necessary to find conditions under which the deactivated alkoxy substituents will take place in the rearrangement reaction. It may be possible to facilitate rearrangement of these molecules by preparing the corresponding silyl enol ethers at low temperature and then raising the temperature to facilitate [3,3]-sigmatropic rearrangement. If this approach is successful the use of chiral boron enolates might also be investigated in order to determine if this approach to asymmetric products can be used, (Scheme 12).



Scheme 12

Also it would be of great interest to study the effectiveness of this rearrangement in the synthesis of many adrenergic antagonist aminoalcohols drugs.[32]

5 This study



31

activated precursor R = aromatic or unsaturated

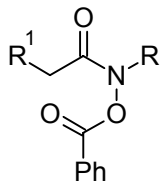
Scheme 13

As we notice from last section in previous work, attempts to rearrange activated and unactivated precursors were successful. However, only a limited number of *N*-methyl-*O*-acyl hydroxamic acids derivatives were prepared..

In this project we report our efforts to facilitate the rearrangement of other activated and unactivated precursors.

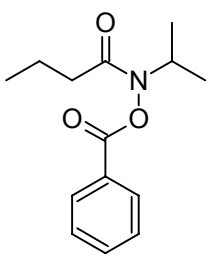
5.1 Preparation of precursors

In order to investigate the effects of the *N*-alkyl substituent upon the rearrangement of activated precursors, a range of hydroxamic acid derivatives of type **32** were prepared.

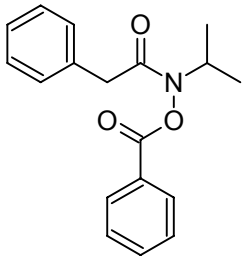


32

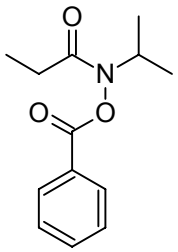
A number of R and R^1 groups were chosen to determine how they would affect the reaction. Hence, the *N*-*i*-Pr derivatives (**32a-32c** and **32e**), and *N*-Bu derived **32f**, and *N*-*n*-Pr derived **32d** were examined. In addition **32** were prepared which contained the benzoyloxy as good leaving group.



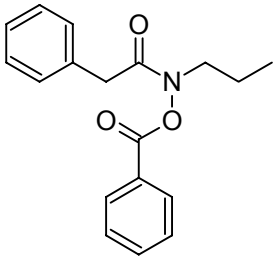
32a



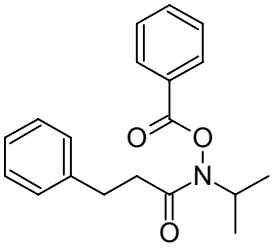
32b



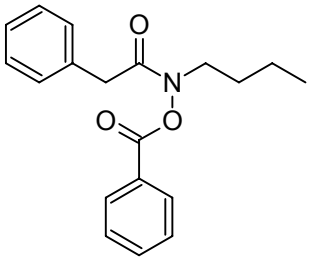
32c



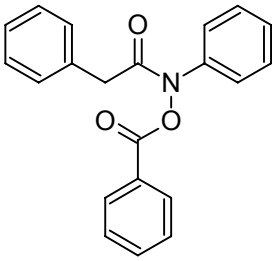
32d



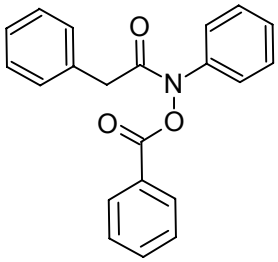
32e



32f



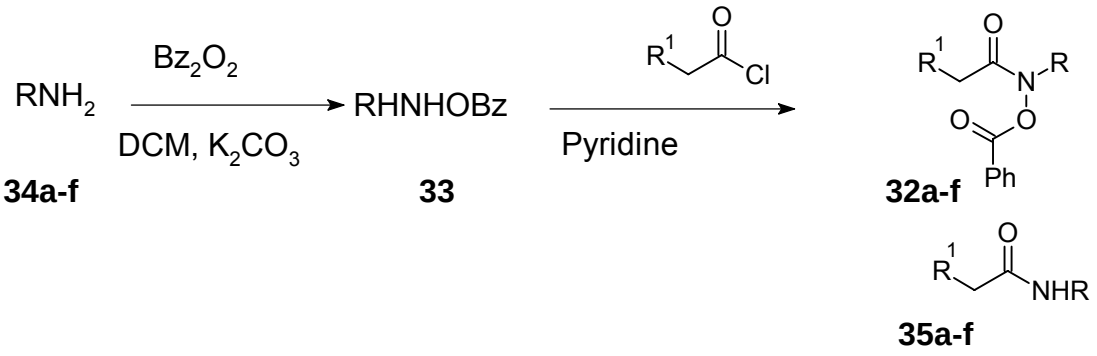
32g



32h

Precursors of type 32

These precursors (**32a-32f**) were prepared by the same method described previously. Hence, the corresponding amines (**34a-f)** were treated with potassium carbonate and dibenzoyl peroxide in refluxing Et_2O. After the appropriate time, (determined by TLC) the white precipitate was filtered off, and pyridine was added to the solution followed by dropwise addition of the acid chloride to give **32a-f**, (Scheme 14) as well as the corresponding amide (**35-a-f**) as a by-product. However, attempts to prepare **32g** and **32h** precursors *via* previous methods were unsuccessful. The yields of these precursors are shown in (Table 1).



34a-f **33** **32a-f** **35a-f**

32a)R = *i*-Pr, R^1= Pr, **32b)**R = *i*-Pr, R^1 = C_6H_4, **32c**)R = *i*-Pr, R^1= Et,

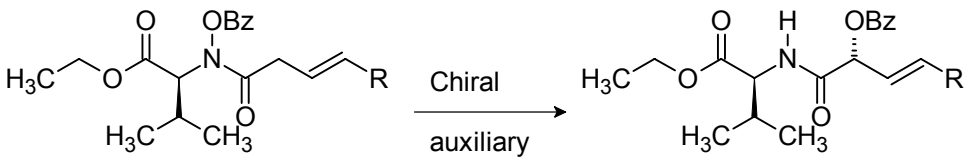
32d) R = n-Pr, R^1 = C_6H_4, **32e**)R = *i*-Pr= R^1 = $(CH_2)C_6H_4$, **32f**) R = n-Bu, R^1 = C_6H_4.

Scheme 14

Table 1 Yields of hydroxamic derivatives (**32 a-f**)

Entry	Compound	R	R^1	Yield (%)
1	**32a**	*i*-Pr	Pr	26
2	**32b**	*i*-Pr	C_6H_4	35
3	**32c**	*i*-Pr	Et	48
4	**32d**	*n*-Pr	C_6H_4	40
5	**32e**	*i*-Pr	$(CH_2)C_6H_4$	41
6	**32f**	*n*-Bu	C_6H_4	74

The attempts to develop an asymmetric variant of these precursors were unsuccessful therefore, we could not investigate chiral variant of this rearrangement.

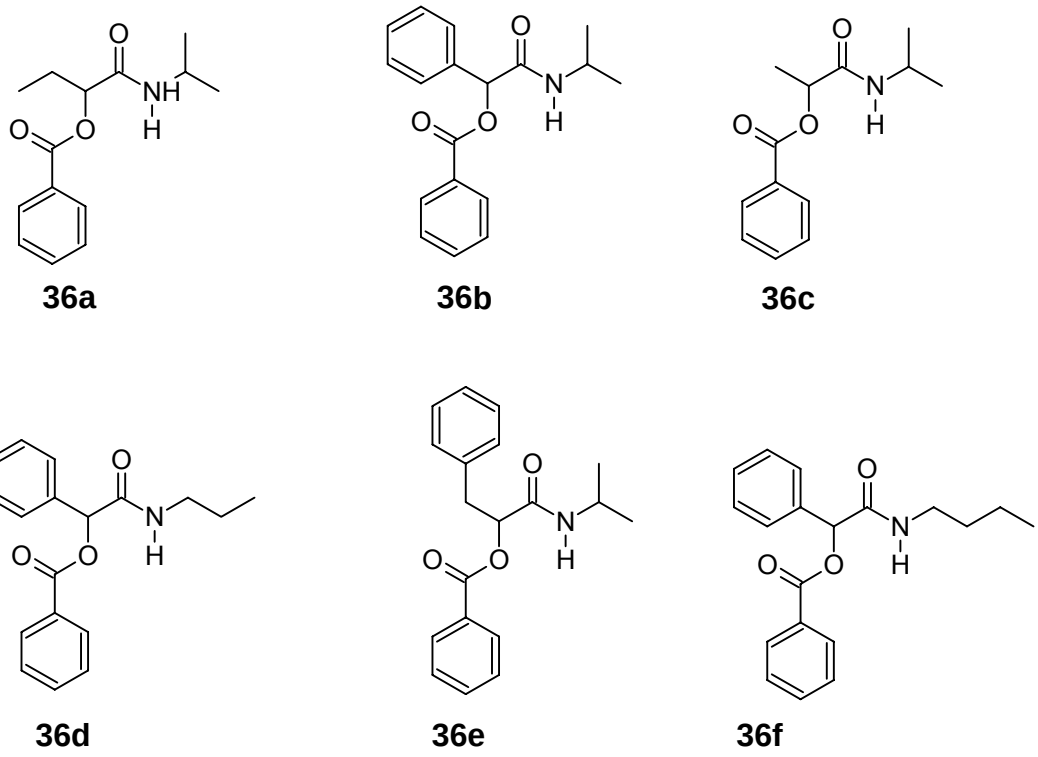


Scheme 15

5.2 The rearrangements reactions

With the precursors (**32a-f)** in hand, their rearrangements reactions were then investigated.

Hence, heating (**32b)** at 110°C in refluxing toluene with (0.2eq) Et_3N for appropriate time (determined by TLC) furnished the desired rearranged product (**36a-f**).



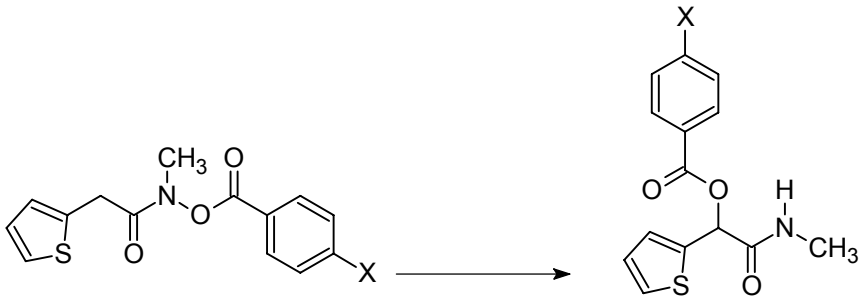
Rearranged products (36a-f)

The crude NMR indicates that the, the isopropyl and the phenylacetyl groups in (**32b**) are the best R and R^1 groups to use respectively, however, the other R and R^1 which were examined were also good enough for successful rearrangement to be observed.

Interestingly, even the rearrangements of unactivated precursors (**32e** and **32c**) also observed,

5.3 Kinetic studies

A kinetic data has been obtained from the investigation of the rearrangement of previously prepared hydroxamic acids derivatives of the type **(37)**, (Scheme 15),



37a-e **38a-e**

a) X = H, **b**) X = NO_2, **c**) X = Cl, **d**) X = Me, **e**) X = MeO

Scheme 16

Hence, the previously prepared precursors **37a-e**[32] were treated with (0.05 eq) Et_3N in toluene at 75°C and the extent of the reaction monitored by ^{1}H NMR. The product distribution as function of time was determined by ^{1}H NMR looking specifically at the integrals of the ^{1}HNMe protons of the products **38a-e** and the starting materials **38a-e**, (Table 2).

Table 2 **^{1}H NMR signals used to estimate concentration**

Compound	X	δ(A)	δ (B)
37a	H	3.31	2.81
37b	NO_2	3.46	2.78
37c	Cl	3.43	2.90
37d	Me	3.32	2.89
37e	MeO	3.31	2.87

δ (A) integrals of the NMe protons of the starting materials. δ (B) integrals of the NMe protons of the products.

The rearrangement was found to follow a simple first order rate law, in which ln $[A_t]$ /$[A_0]$ = **-***kt*. Where $[A_0]$ represents the initial concentration of the hydroxamic acid **37a-e** and $[A_t]$ represents the concentration at the time t. ^{1}H NMR spectroscopy was found to be convenient for measuring the $[A_t]$ from the integrals for signals corresponding to specific protons in the spectra. The NMe protons of the starting materials **37a-e** and products **38a-e** of the rearranged product were convenient for this purpose. The first order rate coefficient of the reference compound **37a** (X = H) k_x was found by plotting the expression ln $[A_t]$ /$[A_0]$ against time (min) elapsed and yielded a straight line (R^2 = 0.9347) as would expected for a first order reaction, (Fig 1).

Table 3 Kinetic data from the rearrangement of 37a

X	Time (min)	[B] ($Mx10^{-3}$)	[A_t]($Mx10^{-3}$)	[A_t] /[A_0]	ln[A_t] /[A_0]
H	0	0	9.40	1	0
	120	0.40	9.00	0.958	-0.0429
	360	4.05	5.35	0.570	-0.5612
	720	5.2	4.20	0.447	-0.8036

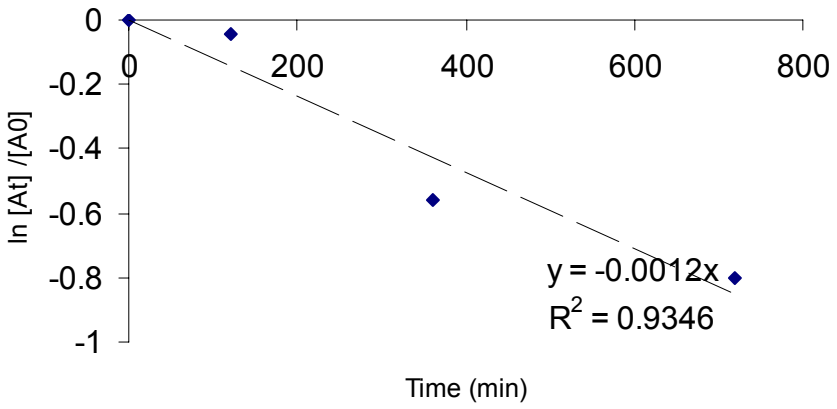


Figure 1 Plot of ln [A_t] /[A_0] vs time for rearrangement of 37a

R^2 = trend line equation, y = -kt, k = rate constant, t = time (min)

The others derivatives were also obtained see (Table 4-7) and (Fig 2-5).

Table 4 Kinetic data from the rearrangement 37b

X	Time (min)	[B] ($Mx10^{-3}$)	[A_t] ($Mx10^{-3}$)	[A_t] /[A_0]	Ln[A_t]/[A_0]
NO_2	0	0	9.40	1	0
	2	1.17	8.23	0.876	-0.1316
	10	1.40	8.00	0.852	-0.1592
	30	2.77	6.63	0.706	-0.3476
	60	3.25	6.15	0.655	-0.4226
	120	6.67	2.73	0.291	-1.234

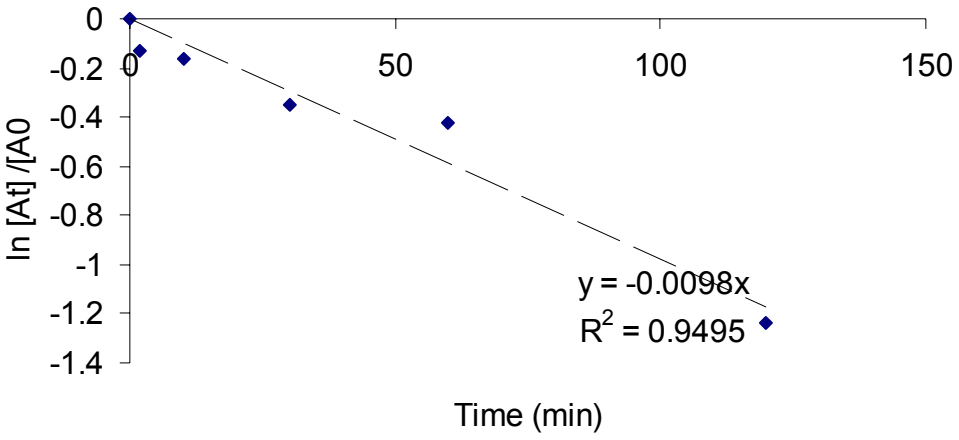


Figure 2.4 Plot of ln [A_t] /[A_0] vs time for rearrangement of 37b

Table 5 Kinetic data from the rearrangement of 37c

X	Time (min)	[B] ($Mx10^{-4}$)	[A_t] ($Mx10^{-3}$)	[A_t] /[A_0]	ln[A_t] /[A_0]
Cl	0	0	9.4	1	0
	2	0.452	8.948	0.952	-0.0485
	10	1.157	8.243	0.877	-0.1304
	30	0.630	8.770	0.933	-0.0690
	160	5.462	3.938	0.419	-0.8668

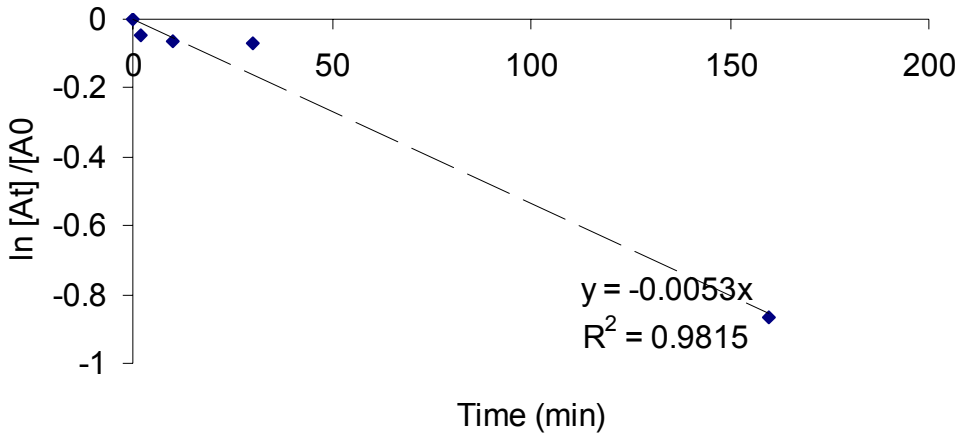


Figure 6 Plot of ln [A_t] /[A_0] vs time for rearrangement of 37c

Table 6 Kinetic data from the rearrangement of 37d

X	Time (min)	[B] ($Mx10^{-4}$)	[A_t] ($Mx10^{-3}$)	[A_t] /[A_0]	ln[A_t] /[A_0]
Me	0	0	9.40	1	0
	120	0.151	9.249	0.984	-0.1120
	240	1.401	7.999	0.851	-0.1602
	3600	9.024	0.376	0.040	-3.198
	4000	9.109	0.291	0.031	-3.450

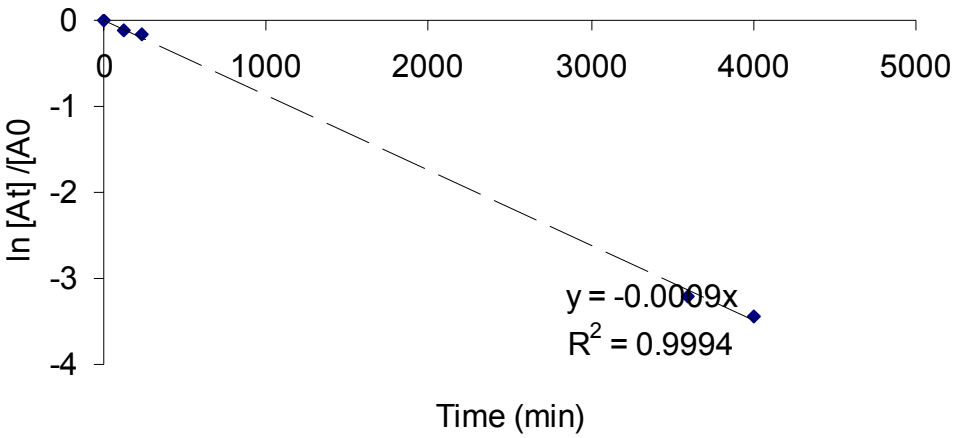


Figure 7 Plot of ln [A_t] /[A_0] vs time for rearrangement of 37d

Table 7 Kinetic data from the rearrangement of 37e

X	Time (min)	[B] ($Mx10^{-4}$)	[A_t] ($Mx10^{-3}$)	[A_t] /[A_0]	ln[A_t] /[A_0]
MeO	0	0	9.40	1	0
	330	1.41	7.99	0.8501	-0.1624
	490	2.02	7.38	0.7852	-0.2418
	600	2.04	7.36	0.7834	-0.2440
	1800	4.12	5.28	0.5625	-0.5752

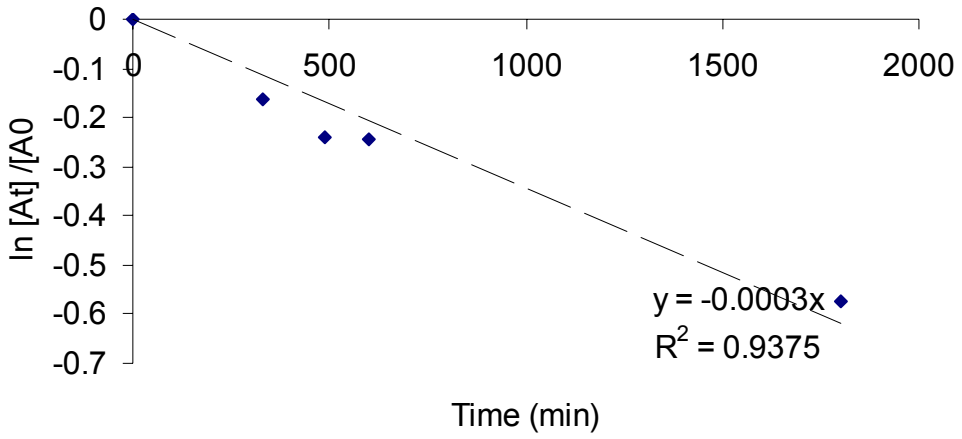


Figure 8 Plot of ln[A_t] /[A_0] vs time for rearrangement of 37e

The reaction's rate were found to follow the following order NO_2 ($k = 98x10^{-4}$ min^{-1}) > Cl ($k = 53x10^{-4}$ min^{-1}) > H ($k = 12x10^{-4}$ min^{-1}) > Me ($k = 9x10^{-4}$ min^{-1})> MeO ($k = 3x10^{-4}$ min^{-1}). Electron-donating groups were found to decrease the reaction's rate whereas electron-withdrawing ones increased the reaction's rate. The nitro group derivative was the fastest reaction ($k = 98x10^{-4}$ min^{-1}) while the methoxy derivative was the slowest ($k = 3x10^{-4}$ min^{-1}

^{1}). The nitro group derivative (k = 98x10^{-4} min^{-1}) is approximately twice as fast as the chloro derivative (k = 54x10^{-4} m^{-1}) while the MeO derivative (k = 3x10^{-4} min^{-1}) is approximately three times slower than the Me derivative (k = 9x10^{-4} min^{-1}), (Table 2.11).

Table 8 Calculated kinetic data of the rearrangements of thienyl hydroxamic acids derivatives 37a-e

X	Rate onstant (x 10^{-4} min-^{1})	Half-life (min) $t_{1/2}$ = ln2/k	$^{a}\sigma_p$	Log k_x/k_H
NO_2	98	70.72	0.78	0.91
Cl	48	144.40	0.23	0.60
H	12	577.62	0	0
Me	9	770.16	-0.17	-0.12
MeO	3	2310.49	-0.27	-0.60

^{a}Note: the values of substituent constants from P. Zuman and R. C. Patel[33]

In similar manner, the half-lives were found to vary systematically from 70.72 min for **37b** (X = NO_2), 130.78 min for **37c** (X = Cl), to 577.62 min in **37a** (X= H), to 770.16 for **37d** (X = Me) and 2310.49 for **37e** (X = MeO). Both half-lives and the reaction's rate reaction indicate, that electron-withdrawing groups accelerate the reaction while the electron-donating group slow the reaction. These substituents effects can be treated quantitatively by use of a linear free energy relationship. The most common used method of such treatment involves the use of Hammett equation which is represent by Log $k_x/k_H = \rho\sigma_x$ where k_x is the rate constant for a compound substituted by group X,

k_H is the rate constant of unsubstituted compound**,** σx is the substituents constant, and ρ is a factor called reaction constant, which remains uncharged for the same reaction under the same conditions.[33] This ρ value is obtained from the slope of the line in log k_x/k_H against the standard σx plot for a reaction series that consist of several substituted compounds.

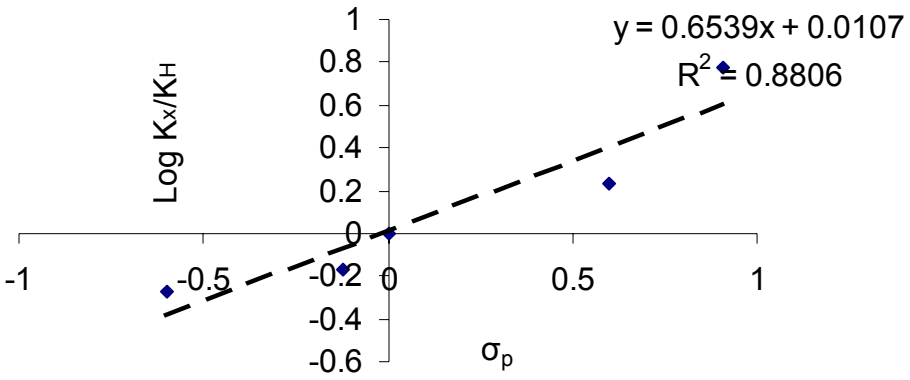
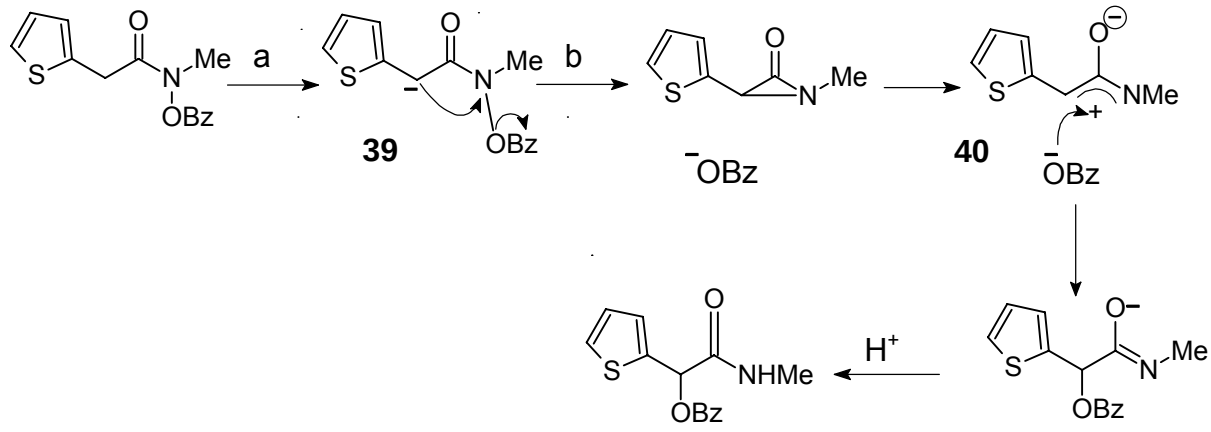


Figure 9 Hammett plot for the rate constant of rearrangements

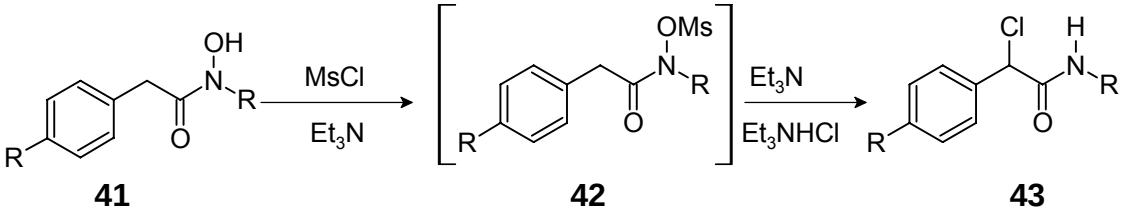
The slope of the correlation line, is referred to as ρ, the reaction constant. It is a measure of sensitivity of the reaction to the electronic substituents effects. As the ρ- (0.65) value is positive this means that a degree of negative charge is built up in the transition state in the rate determining step of the rearrangement. In the light of this result, its less likely that the rate determining step is the loss of the acyloxy group as a carboxylate anion because it might be expected that a ρ value nearer to 1 would arise.

The rate determining step could be either a) deprotonation to form an enolate or b) the loss of the acyloxy group as a carboxylate anion, (Scheme 17).



Scheme 17

This mechanism involves formation of an enol or an enolate followed by nucleophilic displacement of the benzoyloxy group to furnish an α-lactam. After ring opening the α-lactam is trapped *via* the displaced anion (**40**) (which in this example is the benzyloxy anion) to give the rearranged product. This mechanism is similar to that postulated by Hoffman in the reaction of *N*-mesyloxy amides with $Et_3N/Et_3N.HCl$,[34] (scheme 18).

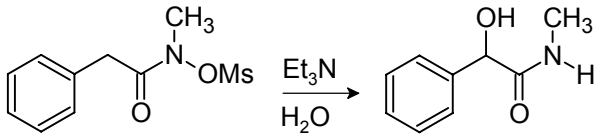


Scheme 18

In Hoffman's reactions *N*-alkylphenylacetohydroxamic acids (**42**) are readily converted to 2-chloro-*N*-alkylphenylacetamides (**43**), (scheme 18).

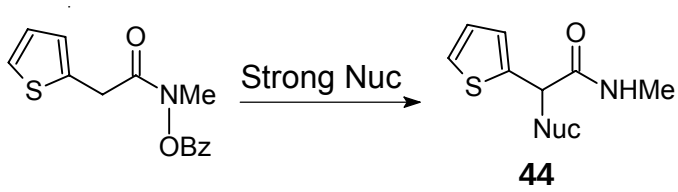
It has been suggested that initial enolate formation and elimination of mesylate furnishes an α-lactam which ring opens to an ion pair and is trapped by chloride to give the 2-substituted-2-chloroamide upon hydrolysis. Evidence for this mechanism was provided when alternative nucleophiles (e.g. H_2O) competitively trapped out the intermediate ion pairs to furnish 2-

substituted-2-hydroxy amides, (Scheme 19) in moderate yields. Other nucleophiles (e.g. I^- and Br^-) were also used to trap the ion pair to give 2-substituted secondary amide products.[35]



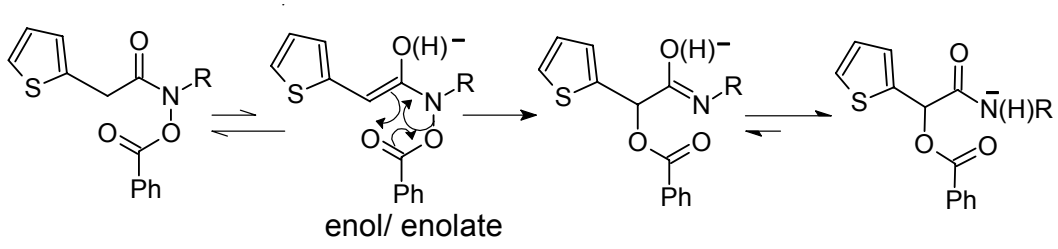
Scheme 19

In contrast when we attempted to trap out the postulated ion pair (**44**) derived from hydroxamic acid (**37**) with other nucleophiles (eg Cl^-) no competitive trapping was detected.



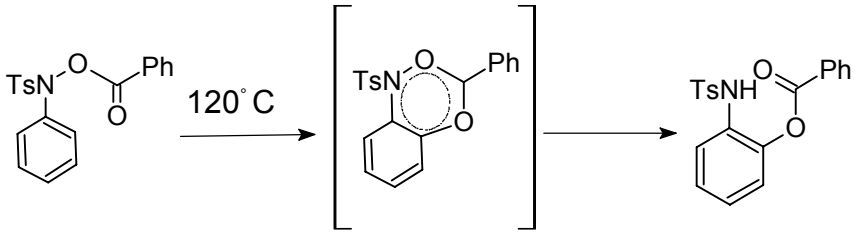
Scheme 20

According to above results, this rearrangement may be a concerted [3,3]-sigmatropic rearrangement of enol (Scheme 21), and the rate limiting step is the formation of the enol or enolate which would become more facile when the acidity of the α-carbonyl protons increased under the inductive effects of the electron withdrawing *O*-acyl groups.



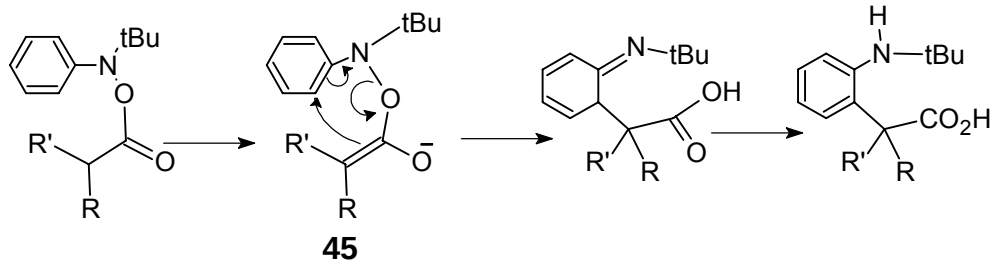
Scheme 21

The negative charge may build up on the oxygen atom of the *N*-*O* bond in the transition state for the reaction. This suggests that the reaction may involve a concerted process. Two related rearrangements have been reported; 1) the thermal rearrangement of *O*-benzoyl-*N*-(4-tolylsulfonyl)-*N*-arylhydroxylamine; in which the transition state and mechanism was found to be heavily dependent upon the substitution pattern of the substrate intermediates, (Scheme 22).[36]



Scheme 22

Or 2) KHMDS mediated anionic [3,3]-sigmatropic rearrangement of the di-enolate or hydroxamic acid derivatives **45**.[37]



45

Scheme 23

5.4 Conclusions

A wide array of potentially useful *O*-acyl hydroxamic acids derivatives can be prepared and rearranged to 2-acyloxyamides good yields *via* treatment with a catalytic amount of Et_3N in dry toluene or DCM.

The positive nature of the reaction's ρ-value reflects that a development of negative charge is built up in rate determining step of the rearrangement which indicates that this rearrangement may proceed *via* a [3,3] sigmatropic rearrangement. Our results have shown the isopropyl and the phenylacetyl groups in (**32b**) are the best R and R^1 groups to use respectively, however, the other R and R^1 which were examined were also good enough for successful rearrangement to be observed.

Interestingly, even the rearrangements of unactivated precursors (**32e** and **32c**) also observed upon treatment with Et_3N, however in less yields.

5.5 Selected Experimental Details

5.5.1 Preparation of precursors

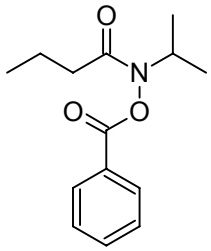
5.5.1.1 General procedure for the preparation of acid chloride

The acid chlorides were prepared directly before use by heating acid at reflux with freshly distilled excess thionyl for 30 min followed by removal of the excess thinly chloride in *vacuo*.

5.5.1.2 General procedure for the preparation of *N*-alkyl-*N*-benzoyloxy-hydroxamic acids derivatives

The appropriate amine (1eq) (0.9 ml, 8.66 mmol), dibenzoyperoxide (1eq), and potassium carbonate were refluxed together in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (1eq) was added followed by dropwise addition of acid chloride. The mixture was refluxed again overnight. The mixture was then diluted with water (100 ml) and the organic phase washed with 10 % HCl (2 x 50 ml), brine (2 x 50 ml) and dried over $MgSO_4$. The product was purified by flash column chromatography (pet.ether-ethylacetate (3:1)).

5.5.1.3 *N*-Benzoyloxy-*N*-*i*-propyl-butaneamide 32c



32a

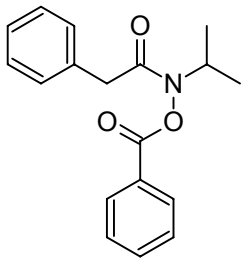
Isopropylamine (0.730 ml, 8.66 mmol), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of butanoyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*i*-propyl-butaneamide **32c** (0.530 g, 26 %) as a colourless oil; (M^+, $C_{14}H_{19}NO_3$) requires: 249.306

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, t, *J* 6.6 Hz, *Me*CH_2), 1.20 (6 H, m, isopropyl), 1.35 (2H, m, $MeCH_2$*CH_2*), 2.95 (2H, two s, CH_2*CH_2*CO), 4.30 (1H, br m, $(Me)_2$*CH*), and 7.44-8.05 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 13.6 (q), 18.2 (2 x q), 22.6 (t), 42.2 (d) 126.9 (s), 128.3 (2 x d), 129.5 (2 x d), 133.2 (d), 163.3 (s), and 170.9 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

5.5.1.4 *N*-Benzoyloxy-*N*-*i*-propyl-phenylacetamide 32b



32b

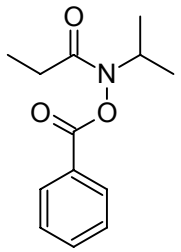
Isopropylamine (0.730 ml, 8.66 mmol), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of phenyl acetyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished ***N***-benzoyloxy-*N*-*i*-propyl-phenylacetamide **32b** (0.88 g, 35 %) as a colourless oil; (M^+, $C_{18}H_{19}NO_3$) requires: 297.348

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (6H, br td, *J* 6.0 & 2.0 Hz, isopropyl), 3.75 (2H, s, PH*CH*$_2$), 4.40 (1H, dd, *J* 6.0 & 2.0 Hz, (Me)$_2$*CH*), and 7.41-8.03 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (2 x q), 22.8 (t), 42.0 (d) 126.9 (s), 128.5 (2 x d), 129.4 (2 x d), 133.7 (d), 167.0 (s), and 170.1 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1765 (OCO), 1663 (NCO), and 1522 (Ar).

5.5.1.5 *N*-Benzoyloxy-*N*-*i*-propyl-propylacetamide 32c



32c

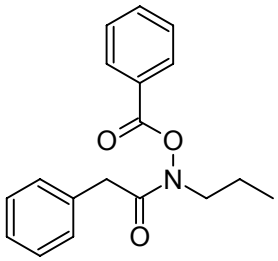
Isopropylamine (0.730 ml, 8.66 mmol), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of propanoyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished ***N***-benzoyloxy-*N*-*i*-propyl-propylacetamide **32c** (0.95 g, 48 %) as a colourless oil; (M^+, $C_{13}H_{17}NO_3$) requires: 235.279

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (3H, t, *J* 6.6 Hz, *Me*CH_2), 0.94 (6 H, d, *J* 6.6 Hz, isopropyl), 2.65 (2H, two s, Me*CH*$_2$), 4.0 (1H, br m, $(Me)_2$*CH*), and 7.17-7.80 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 8.3 (q), 19.2 (2 x q), 22.6 (t), 50.2 (d) 126.9 (s), 128.3 (2 x d), 129.3 (2 x d), 134.3 (d), 166.9 (s), and 169.3 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

5.5.1.6 *N*-Benzoyloxy-*N*-*n*-propyl-phenylacetamide 32d



32d

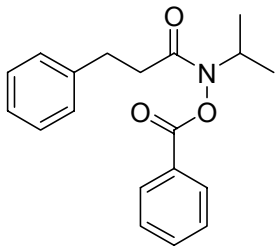
Propylamine (8.66 mmol, 0.710 ml, 0.511g,), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of phenyl acetyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished ***N***-benzoyloxy-*N*-*n*-propyl-phenylacetamide **32d** (1.0 g, 40 %) as a colourless oil; (M^+, $C_{18}H_{19}NO_3$) requires: 297.348

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (3H, t, *J* 7.3 Hz, *Me*CH_2), 1.64 (2 H, septet, *J* 7.3 Hz, Me*CH*$_2$), 3.42 (2H, m, MeCH$_2$*CH*$_2$), 3.72 (2H, s, Ph*CH*$_2$), and 7.30-7.85 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 11.3 (q), 22.6 (t), 41.0 (t), 41 (t), 126.9 (s), 128.4 (2 x d), 129.3 (2 x d), 133.3 (d), 168.4 (s), and 171.7 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

5.5.1.7 *N*-Benzoyloxy-*N*-*i*-propyl-3-phenyl-propioamide 32e



32e

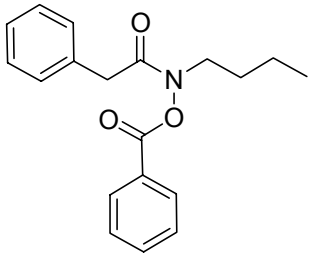
i-Propylamine (0.730 ml, 8.66 mmol), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of 3-phenyl-propionoyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished ***N***-benzoyloxy-*N*-*i*-propyl-3-phenyl-propioamide **32e** (1.1 g, 41 %) as a white crestline ; (M^+, $C_{19}H_{21}NO_3$) requires: 311.1521

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (3H, t, *J* 6.6 Hz, *Me*CH_2), 2.62 (2 H, t, *J* 8.0 Hz, CH_2*CH_2*CO), 2.90 (2H, t, , *J* 8.0 Hz Ph*CH_2* CH_2), and 7.16-7.73 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.8 (q), 30.7 (t), 35.7 (t), 41.0 (t), 42.3 (d), 126.4 (s), 128.4 (2 x d), 128.6 (2 x d), 133.3 (d), 140.3 (s), and 179.1 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

5.5.1.8 *N*-Benzoyloxy-*N*-*n*-butyl-phenyl-acetamidee 32f



32f

n-Butylamine (8.66 mmol, 0.875 ml, 0.631g,), dibenzoylperoxide (2.10 g, 8.66 mmol), and potassium carbonate (1.18 g, 8.66 mmol) were refluxed in Et_2O (30 ml) for 12 h. The formed precipitate was filtered off to give a solution to which pyridine (0.70 ml, 8.66 mmol) was added followed by dropwise addition of phenylacetyl chloride. The mixture was refluxed overnight. Purification by flash column chromatography furnished ***N***-benzoyloxy-*N*-*n*-butyl-phenyl-acetamidee **32f** (2.0 g, 74 %) as a white solid crystals ; (M^+, $C_{19}H_{21}NO_3$) requires: 311.1521

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.860 (3H, t, *J* 7.0 Hz, *Me*CH_2), 1.25-1.30 (2 H, m, Me*CH*$_2$), 1.45-1.54 (2H, m, $MeCH_2$*CH*$_2$), 3.34 (2H, td, *J* 7.0, 2.0 Hz, $PhCH_2$), and 7.16-7.73 (5H, m, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 13.7 (q), 20.0 (t), 31.3 (t), 39.9 (t), 40.0 (t), 126.9 (s), 128.4 (2 x d), 129.3 (2 x d), 133.3 (d), 168.4 (s), and 171.7 (s).

IR ($CHCl_3$, ν_{max} /cm^{-1}) 1763 (OCO), 1662 (NCO), and 1524 (Ar).

5.5.2 The rearrangements reactions

5.5.2.1 General procedure for phosphazene base catalysed rearrangement

To a solution of *N*-benzoyloxy-*N*-alkyl-hydroxamic acid derivatives **32a-f** (1eq) in dry toluene was added Et_3N, then the mixture was refluxed. After the appropriate time water (2 ml) was added and the organic phase was washed with 10 % HCl (1 x 2 ml), brine (1 x 5 ml), and dried over $MgSO_4$. Removal of the solvent in the *vacuo* followed by flash column chromatography (pet.ether-ethylacetate (10:1)) furnished 2-benzoyloxy-*N*-alkyl-hydroxamic acid derivatives **165b-d**.

References

1 E. J. Corey, J. R. Cashman, S. S. Kanter, S. W. Wright, *J. Am. Chem. Soc.,* 1984, **106**, 1303.

2 P. Koza, J. Berriot, *Tetrahedron.,* 1999, **55**, 7221.

3 J. M. Roosenberg, M. J. Miller, *J. Org. Chem*., 2000, **65**, 4838.

4 H. M. Niemeyer, J. M. Jerez, *Heredity.*, 1997, **79**, 10.

5 M. Maski, Y. Chigira, M. Ohta, *J. Org. Chem.*, 1966, **31**, 4143.

6 N. H. Anderson, W. D. Ollis, J. E. Thorpe, A. D. Ward, *J. Chem. Soc. Chem*. *Commun.,* 1974, 420.

7 B. Kurzak, H. Kozlowski, E. Farkas, *Coord. Chem. Rev*., 1992, **114**, 169.

8 R. J. Bergeron, J. S. McManis, O. Phanstiel, J.R.T. Vinson*, J. Org. Chem*., 1995, **60**, 109.

9 J. B. Neilands*. Bacteriol. Rev.*, 1957, **21**, 101.

10 M. J. Miller, *Chem. Rev*, 1989, **89**, 1563.

11 S. M. Payne, *CRC Crit. Rev. Microbiol.*, 1988, **16**, 81.

12 L. R. Weintraub, M. E. Conard, W. H. Crosby, *Med. Clin. N. Am.*, 1966, **50**, 1579.

13 J. B. Summers, J. B. Mazdiyasni, J. H. Holms, J. D. Ratajczyk, R. D. Dyer, J. W. Carter, *J. Med. Chem*., 1987, **30**, 574.

14 B. Summers, K. H. Kim, J. B. Mazdiyasni, J. H. Holms, J. D. Ratajczyk, R. A. O. Stewart, D. Dyer, J. W. Carter, *J. Med. Chem*., 1987, **33**, 992.

15 J. B. Summers, J. B. Mazdiyasni, J. H. Holms, J. D. Ratajczyk, R. D. Dyer, J. W. Carter, *J. Med. Chem*., 1990, **30**, 2121.

16 S. Pikul, K. L. M. Dunham, N. G. Almstead, B. De, M. G. Natchus, M. V. Anastasio, S. J. McPhile, C. E. Snider, Y. O. Taiwo, L. Chen, C. M. Dunaway, F. Cu, G. L. Mieling, *J. Med. Chem*., 1999, **42**, 87.

17 B. Barlaam, T. G. Bird, C. L. Brempt, D. Cambell, S. J. Foster, R. Maciewicz, *J. Med. Chem.,* 1999, **42**, 4890.

18 C. Pyke, E. Ralfkiaer, P. Huhtala, T. Hurskainen, K. Danoe, *Cancer. Res*., 1992, **52**, 1336.

19 Y. K. Agrawal, *Russ. Chem. Rev*. *(Engl. Transl.),* 1979, **48**, 948.

20 R. L. Shriner, C. K. F. Hermann, T. C. Morrill, D. Y. Curtin, R. C. Fuson, *The Systematic Identification of Organic Compounds*, Wiley, London, 1997.

21 A. J. Clark, J. L. Peacock, Y. S. S. Al-Faiyz, *Tetrahedron Lett*. 1998, **39**, 1269

22 Y. S. S. Al-Faiyz, MSc. Theses, *The Rearrangement of Hydroxamic Acid Derivatives.,* University of Warwick, 1998.

23 T. Nogrady, *Medicinal Chemistry,* Oxford University Press, Oxford, 1988.

24 D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. Press, A. C. Ritchie, *J. Med. Chem.,* 1970, **13**, 674.

25 P. Davis and Co., *British Patent*, 1968, **1**, 125 671.

26 S. L. Shapiro, I. M. Rose, L. Freedman, *J. Am. Chem. Soc*., 1959, 6322.

27 P. Beak, D. B. Reitz, *Chem. Rev*., 1978, **78**, 275.

28 K. Smith, K. Swaminathan, *J. Chem. Soc.* 1976, 387.

29 G. L. Grunewald, W. J. Brouillertte, J. A. Finney, *Tetrahedron Lett.,* 1980, **21**, 1219.

30 cholkopf, H. Beckhaus, *Angew. Chem. Int. Ed. Engl*., 1976, **15**, 293.

31 Vedejs, S. Larsen, F. G. West, *J. Org. Chem.* 1985, **50**, 2170.

32 Andrew J. Clark, Y. Al-Fayz, and Michael Brodharast*, J. Chem. Soc*., *Perkin Trans 1*, 2000, 1117-1127.

33 Z, Patel, *Techniques in Organic Reactions Kinetics*, Wiley, Canada, 1984.

34 R.V. Hoffman, N. K. Wenting .*et al*. *J. Org. Chem.* **1993**, *58*, 2355.

35 (A) R.V. Hoffman,.;N.K. Nayyar, *et al*. *J. Org. Chem*. **1992**, *57*, 5700. (B) R. V. Hoffman; B.W Klinekole *et al*,. *J. Am. Chem. Soc.* **1992**, *114*, 6262. (C) R.V. Hoffman,; N. K. Nayyar. *et al. J. Org. Chem.* **1995**, *60*, 7043.

36 S. Oae, T. Sakurai, *Tetrahedron.*, 1976, **32**, 2289.

37 Y. Endo, T. Uchida, S. Hizatate, K. Shudo, *Synthesis.*, 1994, 1096.