Synthesis of New *N*-Alkyl-*O*-Acyl Hydroxamic Acid Derivatives

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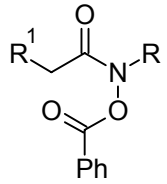
Abstract:

A wide array of useful *N*-alkyl-*O*-acyl- hydroxamic acid derivatives have been prepared. Both aromatic and aliphatic *N*-acyl side chains were tolerated in the preparation methods. The results have shown that the nature of *N*-acyl chains and *N*-alkyl group affects the yields of these products. It has been found that butyl and phenylacetyl groups in (**1f**) are the best R and R^1 groups to use respectively, however the other R and R^1 which were examined were also tolerated for successful preparation to be observed. The yield of these compounds are relatively low, this may be because of competitive formation of by products (**1a-f**).

Key words: Hydroxamic acids, alkylation, amidyl radicals.

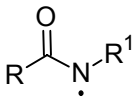
Introduction:

N-alkyl-*O*-acyl hydroxamic acids derivatives (**1**) represent a powerful tool in the synthesis of cyclic and heterocyclic compounds.[1-2] However, their chemistry have been little explored.[2-8]



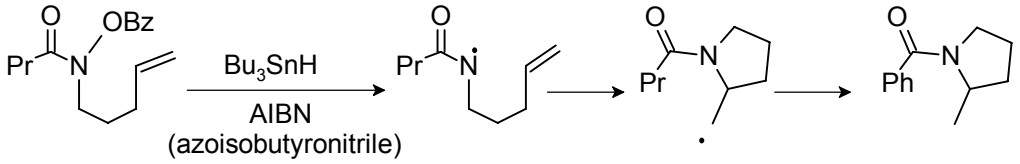
1

The weakness of the *N*-*O* bond in these hydroxamic acid derivatives makes them attractive precursors for the generations of amidyl radicals (**2**) by *N*-*O* homolysis.[2]

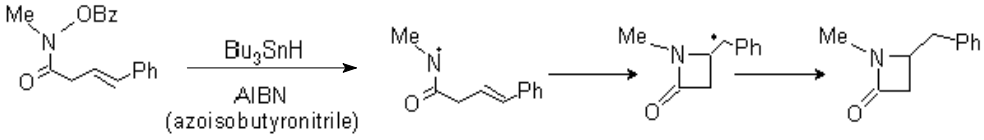


2

In particular *O*-benzoyl hydroxamic acid derivatives have been used as precursors for amidyl radicals (**2**) which undergo cyclisation to give five membered rings,[9] (Scheme **1**), or β-lactams *via* a 4-exo cyclisation process,[10] (Scheme 2).

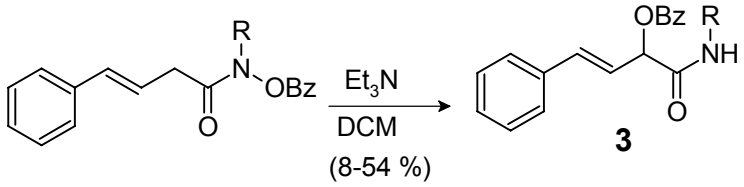


Scheme 1



Scheme 2

The rearrangements of these compounds have also been observed to occur under basic conditions (e.g. Et_3N or tert-butylimino-tri-(pyrrolidino)-phosphorane (BTPP)). The reactions furnished the rearranged compound (**3**) in moderate yield,[8, 11, 12] (Scheme 3).



Scheme 3

A limited number of *N*-methyl-*O*-acyl hydroxamic acid derivatives were prepared.

This work explores the efforts to synthesis a range of a new *N*-methyl-*O*-acyl hydroxamic acids derivatives.

Experimental details

Materials and Methods

Infrared spectra were recorded neat, in a solution cell, on a Perkin-Elmer 1720X Fourier transform spectrometer. ^{1}H NMR spectra were recorded at 300 MHz, on a Bruker DPS300. ^{13}C NMR spectra were recorded at 75MHz on Bruker DPS300. Chemical shifts are quoted in parts per million (ppm), referenced to TMS (0.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Flash chromatography was performed on (Merck Kieselgel $60F_{245}$, 230-400 mesh). TLC was carried out using aluminium backed plates precoated with silica (0.2mm, $60F_{245}$) and were visualised using UV, fluorescence (245nm), phosphomolybdic acid, potassium permanganate solution or dilute sulphuric acid in ethanol. Chemicals were purchased from Sigma-Aldrich, and Lancaster at the highest grade available. Anhydrous solvents were obtained from Sigma-Aldrich.

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

General procedure for preparation of *N*-alkyl-*N*-benzoyloxy-hydroxamic acid derivatives (1a-1f).

The appropriate amine (1eq) (0.9 ml, 8.66 mmol), dibenzoyl peroxide (Bz_2O_2) (1eq), and potassium carbonate were refluxed together in diethylether (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 (silica gel/ petroleumether-ethyl acetate 3:1).

N-Benzoyloxy-*N*-*i*-propyl-butanamide (1a)

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*i*-propyl-butaneamide **1a** (0.530 g, 26 %) as a colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, t, *J* 6.0 Hz, $\underline{Me}CH_2$), 1.2 (6 H, d, *J* 7.0 Hz, isopropyl), 1.35 (2H, sextet, *J* 6.0, $Me\underline{CH_2}CH_2$), 2.30 (2H, t, *J* 6.0 Hz, $CH_2\underline{CH_2}CO$), 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$), and 7.44-8.05 (5H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 13.6 (q), 18.2 (2 x q), 22.0 (t), 22.6 (t), 42.2 (d) 128.3 (2 x d), 129.5 (2

x d), 133.2 (d), 130.3 (s), 163.3 (s), and 170.9 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

***N*-Benzoyloxy-*N*-*i*-propyl-phenylacetamide (1b)**

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*i*-propyl-phenylacetamide **1b** (0.88 g, 35 %) as a colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (6H, br dd, *J* 6.0 & 2.0 Hz, $\underline{(Me)_2}CH$), 3.75 (2H, s, $Ph\underline{CH_2}$), 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$), and 7.41-8.03 (10H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (2 x q), 22.8 (t), 42.0 (d), 127.3 (d), 128.5 (2 x d), 128.7 (2 x d), 129.4 (2 x d), 130.1(2 x d), 130.9 (s), 133.7 (d), 135 (s), 167.0 (s), and 170.1 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1765 (OCO), 1663 (NCO), and 1522 (Ar).

***N*-Benzoyloxy-*N*-*i*-propyl-propanamide (1c)**

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*i*-propyl-propylacetamide **1c** (0.95 g, 48 %) as a colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, t, *J* 7.0 Hz, $\underline{Me}CH_2$), 1.20 (6 H, d, *J* 6.0 Hz, $\underline{(Me)_2}CH$), 4.21 (2H, q, *J* 7.0 Hz, $Me\underline{CH_2}$), 4.30 (1H, m, $(Me)_2\underline{CH}$), and 7.44-8.05 (5H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 8.3 (q), 18.2 (2 x q), 22.6 (t), 42.2 (d) 128.3 (2 x d), 129.9 (2 x d), 130.7 (s), 134.3 (d), 166.9 (s), and 169.3 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

***N*-Benzoyloxy-*N*-*n*-propyl-phenylacetamide (1d)**

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-propyl-phenylacetamide **1d** (1.0 g, 40 %) as a colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (3H, t, *J* 7.3 Hz, $\underline{Me}CH_2$), 1.62 (2 H, sextet, *J* 7.3 Hz, $Me\underline{CH_2}CH_2$), 3.42 (2H, t, *J* 7.3 Hz, $MeCH_2\underline{CH_2}$), 3.72 (2H, s, $Ph\underline{CH_2}$), and 7.30-8.50 (10H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 11.3 (q), 22.6 (t), 34.9 (t), 49.7 (t), 127.8 (d), 128.4 (2 x d), 128.5 (2 x d), 129.4 (2 x d), 129.8 (2 x d), 130.3 (s), 133.3 (d), 135.8 (s), 168.4 (s), and 171.7 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

***N*-Benzoyloxy-*N*-*i*-propyl-3-phenyl-propioamide (1e)**

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*i*-propyl-3-phenyl-propioamide **1e** (1.1 g, 41 %) as a white crestline; mp (120-123°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (6H, d, *J* 6.6 Hz, $\underline{(Me)_2}CH$), 2.62 (2 H, t, *J* 8.0 Hz, $CH_2\underline{CH_2}CO$), 2.90 (2H, t, *J* 8.0 Hz, $Ph\underline{CH_2}CH_2$), 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$), and 7.16-7.73 (10H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz)

δ 18.2 (2 x q), 30.7 (t), 35.7 (t), 42.3 (d), 126.4 (d), 127.9 (2 x d), 128.3 (2 x d), 128.6 (2 x d), 130.1 (2 x d), 130.3 (s), 134.6 (d), 140.3 (s), 164.5 (s), and 169.1 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

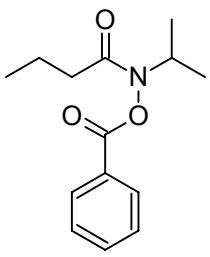
_N_-Benzoyloxy-_N_-_n_-butyl-phenylacetamide (1f)

Purification by flash column chromatography furnished *N*-benzoyloxy-*N*-*n*-butyl-phenyl-acetamidee **1f** (2.0 g, 74 %) as a white solid crystline; mp (132-134°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (3H, t, *J* 7.0 Hz, *Me*CH_2), 1.35-1.40 (2 H, m, Me*CH*$_2$), 1.55-1.64 (2H, m, $MeCH_2$*CH*$_2CH_2$), 3.43 (2H, t, *J* 7.0, $MeCH_2CH_2$*CH*$_2$), 3.72 (2H, s, Ph*CH*$_2$) and 7.30-7.85 (10H, m, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 13.7 (q), 20.0 (t), 29.0 (t), 39.9 (t), 49.1 (t), 127.2 (d), 128.5 (2 x d), 128.6 (2 x d), 129.4 (2 x d), 129.9 (2 x d), 133.7 (s), 134.0 (d), 134.6(s), 168.4 (s), and 171.7 (s). IR ($CHCl_3$, ν_{max} /cm^{-1}) 1763 (OCO), 1662 (NCO), and 1524 (Ar).

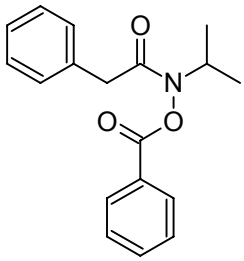
Results and discussion

A range of hydroxamic acid derivatives of type **1** were prepared.

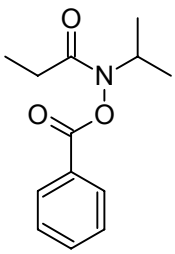
A number of R and R^1 groups were chosen to determine how they would affect the reaction. Hence, the *N*-*i*-Pr derivatives (**1a-c,e**), and *N*-Bu derived **1f**, and *N*-*n*-Pr derived **1d** were examined.



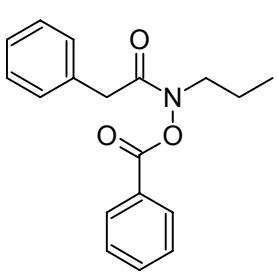
1a



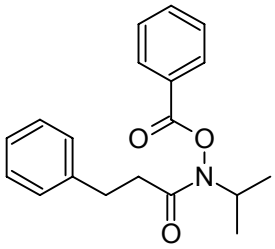
1b



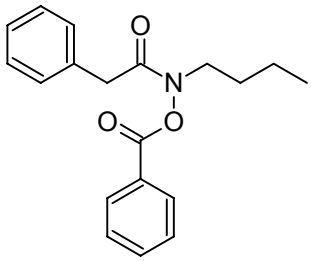
1c



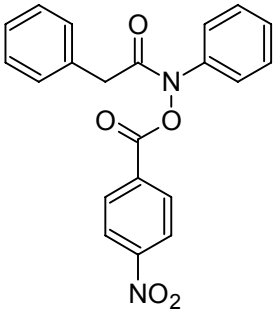
1d



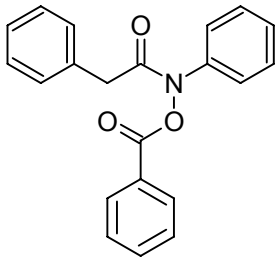
1e



1f

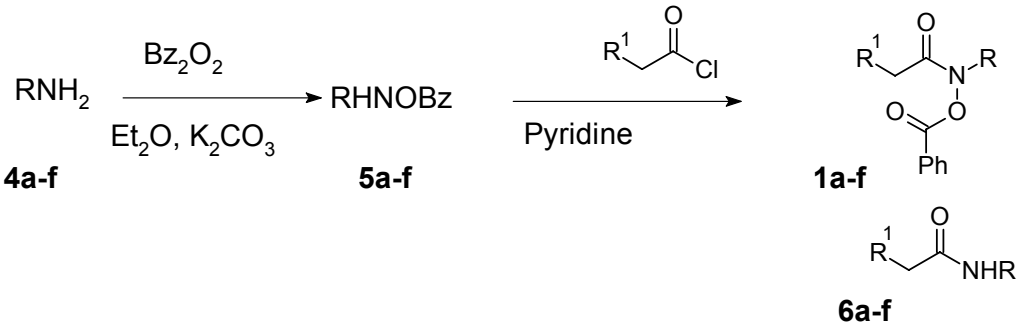


1g



1h

These *N*-alkyl hydroxamic acids **1a-f** were prepared *via* benzoylation of alkyl amines **4a-f** with dibenzoyl peroxide to furnish *O*-benzoylhydroxylamines **5a-f**. Acylation of **5a-f** gives the desired hydroxamic acids (Scheme 4).[13]



4a-f **5a-f** **1a-f** **6a-f**

Scheme 4

Hence, the corresponding amines **4a-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 **1a-f**, (Scheme 4) as well as the corresponding amides **6a-f** as a by-product. Further, attempts to prepare **1g** and **1h** precursors *via* previous methods were unsuccessful. The reason for this failure is not certain but it may be because of the electronic nature of *N*-phenyl group. The yields of these precursors are shown in (Table 1).

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

Entry	Compound	R	R1	Yield (%)
1	1a	i-Pr	Et	26
2	1b	i-Pr	C6H5	35
3	1c	i-Pr	Me	48
4	1d	n-Pr	C6H5	40
5	1e	i-Pr	(CH2)C6H5	41
6	1f	n-Bu	C6H5	74

All compounds exhibited satisfactory spectroscopic and analytical details. IR spectra of these compounds show three major strong and sharp stretching bands at 1774 cm^{-1}, 1663 cm^{-1}, and 1522 cm^{-1}.The band at 1774 cm^{-1} is due to carbonyl group ester (OCO), while bands at 1663 cm^{-1} and 1522 cm^{-1} are due to carbonyl group of tertiary amide and benzene ring respectively. These result is identical to previously reported result of similar compounds.[12]

From the study of ^1H NMR spectra of these compounds, the identical R group shows identical ^1H NMR chemical shift. The R group of **1a-c**, and **1e** is identical (isopropyl group) hence, as expected from the ^1H NMR spectra shows the same chemical shifts for this group as a doublet at δ1.20 and multiplet at δ (4.30-4.39) integrate for the 6 protons, and 1 proton respectively. However, the isopropyl group of **1b** resonate at δ1.20 as broad doublet of doublet (br dd); this spin-spin splitting may be due to coupling of non-equivalent protons. Presumably, free rotation about single bond of isopropyl group in this compound creates different environment to the methyl groups and raise this coupling patterns.

The R group of **1d** representing *n*-propyl resonate as triplet at δ 0.96, sextet at δ1.62, and triplet at δ 4.30 integrated for 3, 2, and 2 protons respectively. While the R group of **1f** resonates as triplet at δ 0.96, multiplet at δ (1.35-140), multiplet at δ (1.55-164), and triplet at δ 3.43 integrates for 3, 2, 2, and 2 protons respectively representing *n*-butyl group.

The methylene group next to R^1 in **1b**, **1d** and **1f** have identical chemical shift at δ 3.72 as a singlet. However, same methylene group in **1a**, and **1e** resonates at δ 2.30 and δ 2.90 respectively. It's clear that aromatic ring (R^1) in **1e** influencing the chemical shift of nearby atoms, so methylene signals are shifted downfield (to higher δ values). The ^{1}H NMR chemical shifts of these compounds are shown in table 2.

Table (2)
^{1}H NMR chemical shifts of of hydroxamic derivatives **1a-f**

	^{1}H NMR		
	R^1	R	$R^1\underline{CH_2}$
a	δ 0.94 (3H, t, *J* 6.6 Hz, $\underline{Me}CH_2$) , and 1.35 (2H, sextet, *J* 6.0 Hz , $MeCH_2$)	δ 1.20 (6H, d, *J* 6, $\underline{(Me)_2}CH$), and 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$))	δ 2.30 (2H, t, J 6.0 Hz)
b	δ 7.41-8.03 (5 H, m, Ph)	δ 1.20 (6H, d, *J* 6, $\underline{(Me)_2}CH$), and 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$))	δ 3.75 (s)
c	δ 0.94 (3H, t, *J* 7.0 Hz,).	δ 1.20 (6H, d, *J* 6, $\underline{(Me)_2}CH$), and 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$))	δ 4.21 (q, *J* 7 Hz)
d	δ 7.41-8.03 (5 H, m, Ph)	δ 0.96 (3H, t 7 Hz, $\underline{Me}CH_2$), 1.62 (2H, sextet, J 7.3, $MeCH_2$), 3.42 (2H, t, J 7.3 Hz, $MeCH_2CH_2$).	δ 3.72 (2H, s)
e	δ 2.90 (2H, t, *J* 8 Hz, $Ph\underline{CH_2}$), and 7.16-7.73 (5H, m, Ph).	1.20 (6H, d, *J* 6.6 Hz, $\underline{(Me)_2}CH$), and 4.30-4.50 (1H, m, $(Me)_2\underline{CH}$))	δ 2.90 (t, *J* 8 Hz).
f	δ 7.30-7.85 (5H, m, Ph)	δ 0.96 (3H, t 7 Hz, $\underline{Me}CH_2$), 1.35-1.40 (2H, m, $MeCH_2$), 1.55-1.64 (2H, m, $MeCH_2CH_2$), 3.43 (2H, t J 7.0 Hz, $MeCH_2CH_2CH_2$)	δ 3.72 (2H, s)

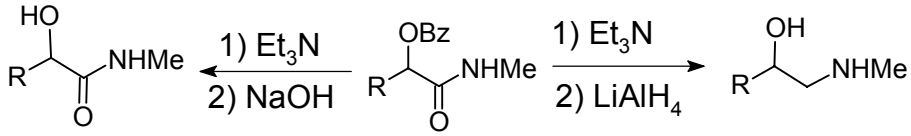
In ^{13}C NMR spectra, ester carbonyl groups resonate between δ163.3-168.5, while the carbonyl groups of the amidic groups resonate between δ 169.3-171.7. The identical R group showed identical resonance at δ 18.2 and 42.2 representing the isopropyl group. While the carbon next to R group in **1b**, **1d** and **1f** resonate at δ 34.9. ^{13}C NMR chemical shifts of these compounds are shown in table 3.

Table (3)
^{13}C NMR chemical shifts of of hydroxamic derivatives **1a-f**

	13C NMR		
	R1	R	$R^1\underline{CH_2}$
a	δ 13.6 (q), and 22.0 (t)	δ 18.2 (2 x q), and 42.2 (d)	δ 22.6 (t)
b	δ 127.3 (d), 129.4 (2 x d), 130.1 (2 x d), and 135 (s).	δ14.1 (2 x q), and 42 (d).	δ34.9 (t)
c	δ 8.3 (q).	δ18.2 (q), and 42.2 (d)	δ 22.6 (t)
d	δ 127.8 (d), 129.4 (2 x d), 129.8 (2 x d), and 135.8 (s).	δ 11.3 (q), 49.7 (t), and 22.63 (t).	δ 34.9 (t)
e	δ 35.7 (t), 126.4 (d), 127.9 (2 x d), 128.3 (2 x d), and 140.3 (s).	18.2 (2 x q), and 42.3 (d).	δ 30.7 (t).
f	δ 127.2 (d), 129.4 (2 x d), 129.5 (2 x d), 134.6 (s).	δ 13.7 (q), 20.0 (t), 29.0 (t), and 49.1(t).	δ 34.9 (t)

Future work

Recent study has demonstrated that these 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 5).[11]



Scheme 5

With these precursors in hands, future study will focus on the investigation of rearrangement of these compounds in more detail in particular to determine which types of precursors would undergo the rearrangement and under which conditions. Also it would be of great interest to study the effectiveness of this rearrangement in the synthesis of many adrenergic antagonist aminoalcohol drugs and their analogous. Accurate kinetic measurement and analysis using Hammett parameters would shed light into the mechanism of the process.

Conclusions:

A wide array of potentially useful *O*-acyl- hydroxamic acid derivatives can be prepared. Results have shown that the butyl and phenylacetyl groups in (**1f**) are the best R and R^1 groups to use respectively. However, the other R and R^1

which have been examined were also good enough for successful preparation to be observed. The yield of these compounds is relatively low which ascribed to competitive formation of by products (**6a-f**)

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تحضير مجموعة جديدة من مشتقات حمض الهايدروكساميك الأسيلية ذات الأتصال بمجموعة الكيل في ذرة النيتروجين الطرفية (*N*-Alkyl-*O*-Acyl Hydroxamic Acids)

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الملخص :

مجموعه جديده واسعه من مشتقات (***N*-alkyl-*O*-acyl hydroxamic acids**) تم تحضيرها وقد شملت هذه المجموعة مشتقات تحتوي على سلسلة طرفيه اسيليه عطريه أو اليفاتيه، وقد أظهرت النتائج أن طبيعة المجموعة المكونة للسلسلة الأسيلية وكذلك المجموعة الألكيلية المتصلة بذرة النيتروجين تؤثران على معدل تكون هذه المركبات، ولهذا فأن مجموعة البيوتيل ومجموعة الفينيل اسيتيل في المركب (**1f**) هي أفضل مجموعتين تستخدمان تواليا في الموقع R و R^1. ومع ذلك فإن جميع المجموعات التي تم اختبارها أعطت نتائج ايجابية. وقد لوحظ انخفاض في معدل تكون هذه المركبات بشكل عام وذلك قد يكون بسبب التكون التنافسي للمركب الجانبي (**1a-f**).