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

Yasair S. Al-Faiyz
Department of Chemistry, College of Science
King Faisal University
Hassa, Saudi Arabia

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 $R'$ groups to use respectively; however, the other $R$ and $R'$ 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.$^{(2-8)}$

![Diagram 1](image1)

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.$^{(2)}$

![Diagram 2](image2)
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 \(\beta\)-lactams via a 4-exo cyclisation process,\(^{(10)}\) (Scheme 2).

The rearrangements of these compounds have also been observed to occur under basic conditions (e.g. Et\(_3\)N or tert-butylimino-tri-(pyrrolidino)-phosphorane (BTPP)). The reactions furnished the rearranged compound (3) in moderate yield,\(^{(8,11,12)}\) (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$_2$O$_2$) (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-butanamide 1a (0.530 g, 26 %) as a colourless oil; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.94 (3H, t, $J$ 6.0 Hz, MeCH$_2$), 1.2 (6 H, d, $J$ 7.0 Hz, isopropyl ), 1.35 (2H, sextet, $J$ 6.0, MeCH$_2$CH$_2$), 2.30 (2H, t, $J$ 6.0 Hz, CH$_2$CH$_2$CO), 4.30-4.50 (1H, m, (Me)$_2$CH), and 7.44-8.05 (5H, m, Ph). $^{13}$C NMR (CDCl$_3$, 62.9 MHz) $\delta$ 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 (CHCl₃, νₘₐₓ/cm⁻¹) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

**N-Benzoyloxy-\textit{N}-\textit{i}-propyl-phenylacetamide (1b)**

Purification by flash column chromatography furnished \textit{N}-benzoyloxy-\textit{N}-\textit{i}-propyl-phenylacetamide 1b (0.88 g, 35 %) as a colourless oil; \textit{¹}H NMR (CDCl₃, 300 MHz) δ 1.20 (6H, br dd, J 6.0 & 2.0 Hz, (Me)₂CH), 3.75 (2H, s, PhCH₂), 4.30-4.50 (1H, m, (Me)₂CH), and 7.41-8.03 (10H, m, Ph). \textit{¹³}C NMR (CDCl₃, 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 (CHCl₃, νₘₐₓ/cm⁻¹) 1765 (OCO), 1663 (NCO), and 1522 (Ar).

**N-Benzoyloxy-\textit{N}-\textit{i}-propyl-propanamide (1c)**

Purification by flash column chromatography furnished \textit{N}-benzoyloxy-\textit{N}-\textit{i}-propyl-propanamide 1c (0.95 g, 48 %) as a colourless oil; \textit{¹}H NMR (CDCl₃, 300 MHz) δ 0.94 (3H, t, J 7.0 Hz, MeCH₂), 1.20 (6H, d, J 6.0 Hz, (Me)₂CH), 4.21 (2H, q, J 7.0 Hz, MeCH₂), 4.30 (1H, m, (Me)₂CH), and 7.44-8.05 (5H, m, Ph). \textit{¹³}C NMR (CDCl₃, 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 (CHCl₃, νₘₐₓ/cm⁻¹) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

**N-Benzoyloxy-\textit{N}-\textit{n}-propyl-phenylacetamide (1d)**

Purification by flash column chromatography furnished \textit{N}-benzoyloxy-\textit{N}-\textit{n}-propyl-phenylacetamide 1d (1.0 g, 40 %) as a colourless oil; \textit{¹}H NMR (CDCl₃, 300 MHz) δ 0.96 (3H, t, J 7.3 Hz, MeCH₂), 1.62 (2H, sextet, J 7.3 Hz, MeCH₂CH₂), 3.42 (2H, t, J 7.3 Hz, MeCH₂CH₂), 3.72 (2H, s, PhCH₂), and 7.30-8.50 (10H, m, Ph). \textit{¹³}C NMR (CDCl₃, 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 (CHCl₃, νₘₐₓ/cm⁻¹) 1764 (OCO), 1663 (NCO), and 1522 (Ar).

**N-Benzoyloxy-\textit{N}-\textit{i}-propyl-3-phenyl-propioamide (1e)**

Purification by flash column chromatography furnished \textit{N}-benzoyloxy-\textit{N}-\textit{i}-propyl-3-phenyl-propioamide 1e (1.1 g, 41 %) as a white crestline; mp (120-123 °C). \textit{¹}H NMR (CDCl₃, 300 MHz) δ 1.20 (6H, d, J 6.6 Hz, (Me)₂CH), 2.62 (2H, t, J 8.0 Hz, CH₂CH₂CO), 2.90 (2H, t, J 8.0 Hz, PhCH₂CH₂), 4.30-4.50 (1H, m, (Me)₂CH), and 7.16-7.73 (10H, m, Ph). \textit{¹³}C NMR (CDCl₃, 62.9 MHz)
\( \delta \) 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\(_3\), \( \nu_{\text{max}} / \text{cm}^{-1} \)) 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 cristline; mp (132-134°C). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 0.96 (3H, t, \( J \) 7.0 Hz, MeCH\(_2\)), 1.35-1.40 (2 H, m, Me\( CH_2 \)), 1.55-1.64 (2H, m, Me\( CH_2\)CH\(_2\)), 3.43 (2H, t, \( J \) 7.0, Me\( CH_2\)CH\(_2\)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) \( \delta \) 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\(_3\), \( \nu_{\text{max}} / \text{cm}^{-1} \)) 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.
These N-alkyl hydroxamic acids 1a-f were prepared via benzylation 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).\(^{(13)}\)
Hence, the corresponding amines 4a-f were treated with potassium carbonate and dibenzoyl peroxide in refluxing Et₂O. 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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>R1</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>i-Pr</td>
<td>Et</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>i-Pr</td>
<td>C₆H₅</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>i-Pr</td>
<td>Me</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>n-Pr</td>
<td>C₆H₅</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>i-Pr</td>
<td>(CH₂)C₆H₅</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>n-Bu</td>
<td>C₆H₅</td>
<td>74</td>
</tr>
</tbody>
</table>

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 results are identical to previously reported results 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 \( \delta 0.96 \), sextet at \( \delta 1.62 \), and triplet at \( \delta 4.30 \) integrated for 3, 2, and 2 protons respectively. While the R group of 1f resonates as triplet at \( \delta 0.96 \), multiplet at \( \delta (1.35-140) \), multiplet at \( \delta (1.55-164) \), and triplet at \( \delta 3.43 \) 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 \( \delta 3.72 \) as a singlet. However, same methylene group in 1a, and 1e resonates at \( \delta 2.30 \) and \( \delta 2.90 \) respectively. It’s clear that aromatic ring (R1) in 1e influencing the chemical shift of nearby atoms, so methylene signals are shifted downfield (to higher \( \delta \) values). The \(^1\)H NMR chemical shifts of these compounds are shown in table 2.

<table>
<thead>
<tr>
<th>Table (2)</th>
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</thead>
</table>

\(^1\)H NMR chemical shifts of hydroxamic derivatives 1a-f

<table>
<thead>
<tr>
<th>( ^1)H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R )</td>
</tr>
<tr>
<td>( a )</td>
</tr>
<tr>
<td>( b )</td>
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<tr>
<td>( c )</td>
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<td>( d )</td>
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<td>( e )</td>
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<tr>
<td>( f )</td>
</tr>
</tbody>
</table>

In \(^{13}\)C NMR spectra, ester carbonyl groups resonate between \( \delta 163.3-168.5 \), while the carbonyl groups of the amidic groups resonate between \( \delta 169.3-171.7 \). The identical R group showed identical resonance at \( \delta 18.2 \) and 42.2 representing the isopropyl group. While the carbon next to R group in 1b, 1d and 1f resonate at \( \delta 34.9 \). \(^{13}\)C NMR chemical shifts of these compounds are shown in table 3.

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**Table (3)**

<table>
<thead>
<tr>
<th></th>
<th>13C NMR chemical shifts of hydroxamic derivatives 1a-f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1</td>
</tr>
<tr>
<td>a</td>
<td>δ 13.6 (q), and 22.0 (t)</td>
</tr>
<tr>
<td>b</td>
<td>δ 127.3 (d), 129.4 (2 x d), 130.1 (2 x d), and 135 (s).</td>
</tr>
<tr>
<td>c</td>
<td>δ 8.3 (q).</td>
</tr>
<tr>
<td>d</td>
<td>δ 127.8 (d), 129.4 (2 x d), 129.8 (2 x d), and 135.8 (s).</td>
</tr>
<tr>
<td>e</td>
<td>δ 35.7 (t), 126.4 (d), 127.9 (2 x d), 128.3 (2 x d), and 140.3 (s).</td>
</tr>
<tr>
<td>f</td>
<td>δ 127.2 (d), 129.4 (2 x d), 129.5 (2 x d), 134.6 (s).</td>
</tr>
</tbody>
</table>

**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](image)

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)

Acknowledgements

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References

تحضير مجموعة جديدة من مشتقات حمض الماييدوكاسكيميك الأساسية ذات الاتصال بمجموعة
(N-Alkyl-O-Acyl Hydroxamic Acids)

ياسر بن سليمان الغانم
قسم الكيمياء - كلية العلوم - جامعة الملك فيصل
الأحساء - المملكة العربية السعودية

الملخص:

(1-{N-alkyl-O-acyl hydroxamic acids}) مجموعة جديدة واسعة من مشتقات تم تحضيرها وقد شملت هذه المجموعة مشتقات تحتوي على سلسلة طرفية اسليه عطرية أو
اليفافية. وقد أظهرت النتائج أن طبيعة المجموعة المحكمة للسلسلة الأسليه وعدها
المجموعة الأسليه المتصلة بذرة النيتروجين تؤثر عن معدل تكون هذه المركبات.
ولذا فإن مجموعة البوتيل ومجموعة الفينيل استبدل بـ R1 & المركب (1f) هي أفضل
مجموعتين تستخدمان توالياً في الموقع R1 وR. ومع ذلك فإن جميع المجموعات التي تم
اختيارها أعطت نتائج إيجابية. وقد لوحظ انخفاض في معدل تكون هذه المركبات
بشكل عام وذلك قد يكون بسبب التحكم التنافسي للمركب الجنبي (1a-f).