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An Improved Synthesis of N-Alkoxy-α-Oxo-Arylacetamides

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AN IMPROVED SYNTHESIS OF N-ALKOXY-α-OXO-ARYLACETAMIDES

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Abstract: The title compounds can be prepared in good yields in a one-pot procedure from arylglyoxylic acid chlorides, 2-pyridone and O-alkylhydroxylamines.

N-Alkoxy-α-oxocarboxamides (**4**) are valuable intermediates for the synthesis of O-alkylglycolohydroxamic acids which have proven to be versatile building blocks for a variety of heterocyclic systems[1]. Unfortunately, the synthesis of the compounds **4** by conventional methods (e.g. aminolysis of α-oxocarboxylic esters, dicyclohexylcarbodiimide coupling of α-oxocarboxylic acids or reaction of the corresponding acid chlorides with O-alkylhydroxylamines) is complicated by the concomitant oximation of the keto group and yields of **4** are generally low. As previously shown[2], this side reaction can be circumvented by transforming an arylglyxoxylic acid by means of Steglichs reagent[3] into the "activated ester" of 3,4-Dihydroxy-2,5-diphenylthiophene 1,1-dioxide, which is smoothly cleaved by the action of alkoxyamines to give **4** in satisfactory yields. However, this procedure requires a multistep preparation of Steglichs reagent which is time-consuming and needs the highly toxic phosgene as a building block. This prompted us to develop a more practical and economical approach to the title compounds that would be amenable to multigram scale operations. With regard to the documented high reactivity of 2-pyridyl esters[4], due to the pronounced nucleofugacity of 2-hydroxypyridine, we envisioned the 2-pyridyl arylglyoxylates **3** as suitable intermediates for the preparation of **4**.

As outlined herein this approach offers indeed a simple and efficient access to the title compounds. Reaction of the arylglyoxylic acid chlorides **2** (prepared from the corresponding arylglyoxylic acids **1** and thionyl chloride according to standard procedures)) with 2-pyridone and triethylamine in dichloromethane at low temperature gave the 2-pyridyl arylglyoxylates **3** which without isolation[5] were allowed to react with the appropriate alkoxyamines at ambient temperature to afford the desired **4a-i** in overall yields of 63-72%.

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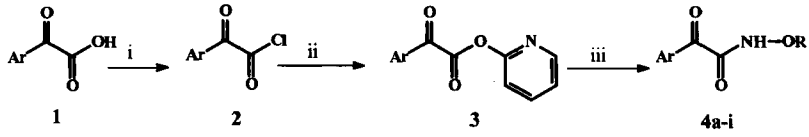
No concurrent oximation of the keto group could be observed under these reaction conditions, indicating a selective attack of the alkoxyamine at the activated ester function. After removal of triethylammonium chloride and 2-pyridone from the reaction mixture by washing with dilute hydrochloric acid and sodium bicarbonate solution and evaporation of the organic solvent most of the herein described **4** were obtained as crystalline compounds. Oily residues could be crystallized from diethyl ether / petrolether on standing in the refrigerator.



1 2 3 4a-i

i: $SOCl_2$; ii: 2-pyridone, $N(C_2H_5)_3$; iii: H_2NOR

1-4	Ar	R
a	phenyl	tbutyl
b	phenyl	ethoxymethoxy
c	4-phenoxyphenyl	methyl
d	4-Cl-phenyl	benzyl
e	4-cyclohexylphenyl	methyl
f	4-methoxyphenyl	methyl
g	4-methoxyphenyl	benzyl
h	2-thienyl	methyl
i	4-F-phenyl	allyl

In conclusion this "one-pot" preparation of the N-alkoxy-α-oxo-arylacetamides **4** is a simple and straight-forward process which reflects the high reactivity of 2-pyridyl esters toward N-nucleophiles. Whether the 2-pyridyl arylglyoxylates **3** can be transformed in an analogous manner to the corresponding hydrazides and N-hydroxyamides is now under investigation.

Experimental

All melting points (uncorrected) were taken in open capillary tubes using a Mettler FP 62 apparatus. ^{1}H-NMR spectra were recorded on a Bruker AC 250 P spectrometer with TMS as the internal standard. The IR-spectra (KBr) were recorded on a Philips Unicam SP 3 200.

General Procedure for the Preparation of N-Alkoxy-α-oxo-arylacetamides 4a-i

To a stirred solution of 4.75g (50 mmoles) of 2-pyridone and 6.06g (60 mmoles) of triethylamine in 25 ml of anhydrous dichloromethane was added dropwise a solution of the freshly prepared arylglyloxylic acid chloride **2** (50 mmoles) in 75 ml anhydrous

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dichloromethane, the temperature beeing kept at 0-5°C. After stirring for 10 minutes at ambient temperature a solution of the appropriate O-alkylhydroxylamine (50 mmoles, 10 ml anhydrous dichloromethane) was added and stirring was continued for 20 minutes. 100 ml diethyl ether were added and the mixture extracted twice with 10 ml 3 *N* hydrochloric acid, followed by 10 ml saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and evaporated. Oily residues crystallized from 10 ml diethyl ether / petrolether (1:1) within two days on standing in the refrigerator.
A single recrystallization from diethyl ether / petrolether furnished pure **4a-i.**

N-tert-Butoxy-α-oxo-phenylacetamide (4a)
From phenylglyoxylic acid and tert-butoxyamine in 66% yield; m.p 100°C; IR: 3160 (NH), 1685, 1660 cm^{-1} (C=O); ^{1}H-NMR(DMSO-d_6): δ 1.25 (s, 3H), 7.46-8.00 (m, 5 aromatic H), 11.42 (s, NH); Anal. Calcd for $C_{12}H_{15}NO_3$ C, 65.14; H, 6.83; N, 6.33. Found C, 65.03; H, 6.76; N, 6.62.

N-Ethoxymethoxy-α-oxo-phenylacetamide (4b)
From phenylglyoxylic acid and ethoxymethoxyamine in 67% yield; m.p. 45°C; IR: 3320 (NH), 1685, 1655 cm^{-1} (C=O); ^{1}H-NMR(DMSO-d_6): δ 1.18 (t, 3H), 3.76 (t, 2H), 4.94 (s, 2H), 7.52-8.06 (m, 5 aromatic H), 12.00 (s, NH); Anal. Calcd. for $C_{11}H_{13}NO_4$ C, 59.19; H, 5.87; N, 6.27. Found C, 59.18; H, 5.90; N, 6.50.

N-Methoxy-α-oxo-4-phenoxyphenylacetamide (4c)
From 4-phenoxyphenylglyoxylic acid and methoxyamine in 63% yield; m.p.74°C; IR: 3200 (NH), 1650 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$): δ 3.88 (s, 3H), 6.95-8.39 (m, 9 aromatic H), 9.48 (s, NH); Anal.Calcd. for $C_{15}H_{13}NO_4$ C, 66.41; H, 4.83; N, 5.61. Found C, 66.31 ; H, 4.86; N, 5.39.

N-Benzyloxy-4-chloro-α-oxo-phenylacetamide (4d)
From 4-chlorophenylglyoxylic acid and benzyloxyamine in 69% yield; m.p. 69°C; IR: 3180 (NH), 1680, 1650 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$) δ 5.00 (s, 2H), 7.30-8.30 (m, 9 aromatic H); Anal.Calcd. for $C_{15}H_{12}ClNO_3$ C, 62,19; H, 4.17; N, 4.83. Found C, 62.05; H, 4.30; N, 5.09.

4-Cyclohexyl-N-methoxymethoxy-α-oxo-phenylacetamide (4e)
From 4-cyclohexylphenylglyoxylic acid and methoxymethoxyamine in 72% yield; m.p.77°C; IR: 3180 (NH), 1690, 1660 cm^{-1} (C=O); ^{1}H-NMR(DMSO-d_6) δ 1.18-1.89 (m, 10H), 2.50-2.69 (m, 1H), 3.48 (s, 3H), 4.95 (s, 2H), 7.46-7.60 (m, 2 aromatic H), 7.90-7.94 (m, 2 aromatic H), 12.09 (s, NH); Anal. Calcd. for $C_{16}H_{21}NO_4$ C, 65.96; H, 7.26; N, 4.81. Found C, 65.72; H, 7.21; N, 4.97.

N,4-Dimethoxy-α-phenylacetamide (4f)
From 4-methoxyphenylglyoxylic acid and methoxyamine in 63% yield; m.p. 93°C; IR: 3180 (NH), 1675, 1640 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$): δ 3.88 (s, 3H), 3.89 (s, 3H), 6.93-7.00 (m, 2 aromatic H), 8.30-8.39 (m, 2 aromatic H), 9.57 (s, NH); Anal.Calcd. for $C_{10}H_{11}NO_4$ C, 57.41; H, 5.30; N, 6.70. Found C, 57.52; H, 5.35; N, 6.72.

N-Benzyloxy-4-methoxy-α-oxo-phenylacetamide (4g)
From 4-methoxyphenylglyoxylic acid and benzyloxyamine in 69% yield; m.p. 82°C; IR: 3310 (NH), 1690, 1640 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$) δ 3.89 (s, 3H), 5.02 (s. 2H), 6.93-8.35 (m, 9

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aromatic H), 9.35 (s, NH); Anal. Calcd. for $C_{16}H_{15}NO_4$ C, 67.36; H, 5.30; N, 4.91. Found C, 67.17; H, 5.23; N, 5.25.

N-Methoxy-α-oxo-2-thienylacetamide (4h)
From 2-thienylglyoxylic acid and methoxyamine in 66% yield; m.p. 122°C; IR: 3200 (NH), 1675, 1640 cm^{-1} (C=O); ^{1}H-NMR($CDCl_3$) δ 3.88 (s, 3H), 7.22 (m, 1H), 7.88 (m, 1H), 8.45 (m, 1H), 9.70 (s, NH); Anal. Calcd. for $C_7H_7NO_3S$ C, 45.50; H, 3.81; N, 7.56. Found C, 45.28; H, 3.82; N, 7.46.

N-Allyloxy-4-fluoro-α-oxo-phenylacetamide (4i)
From 4-fluorophenylglyoxylic acid and allyloxyamine in 65 % yield; m.p. 39°C; IR: 3200 (NH), 1690, 1665 cm^{-1} (C=O); ^{1}H-NMR(DMSO-d_6) δ 4.46 (d, 2H), 5.26-5.48 (m, 2H), 5.78-6.27 (m, 1H), 7.30-7.56 (m, 2 aromatic H), 7.99-8.19 (m, 2 aromatic H), 12.07 (s, NH); Anal. Calcd. for $C_{11}H_{10}FNO_3$ C, 59.19; H, 4.52; N, 6.28. Found C, 59.13; H, 4.59; N, 6.49.

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5. The existence of **3** in the reaction mixture followed from the IR-spectra which showed the (C=O)-stretching band of the ester group in accordance with literature reports at 1760-1770 cm^{-1} [4a,6].

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