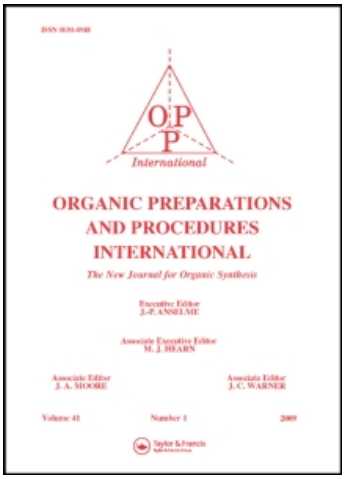

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SYNTHESIS OF N-SUBSTITUTED 2-ALKYL-4-ARYLOXAZOLE-5-CARBOXAMIDES

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6. Less reactive halides, such as *n*-butyl iodide, gave lower yields (60%).

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SYNTHESIS OF N-SUBSTITUTED 2-ALKYL-4-ARYLOXAZOLE-5-CARBOXAMIDES

Submitted by (11/06/91)

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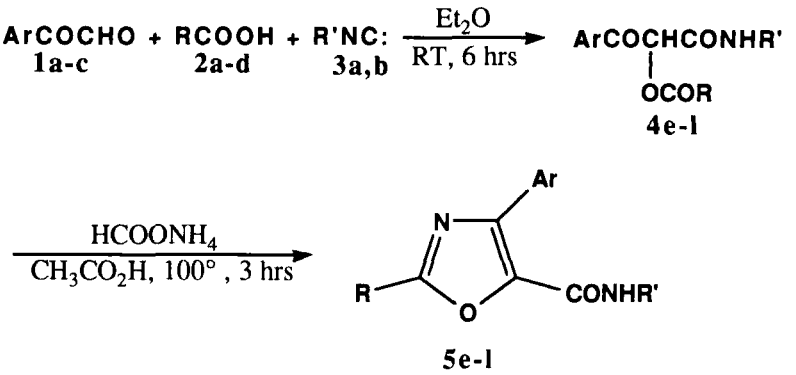
In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides,[1-4] we recently reported the synthesis of *N*-substituted 2,4-diaryloxazole-5-carboxamides.[5] The first step of this synthesis consisted in the preparation of *N*-substituted 2-acyloxy-3-oxoarylpropionamides which were cyclized to *N*-substituted 2,4-diaryloxazole-5-carboxamides upon treatment with ammonium formate in acetic acid. Similar oxazole syntheses have been little investigated[6,7] because the starting α-acyloxy-β-ketoesters are not readily available. In contrast, a wide variety of *N*-substituted α-acyloxy-β-ketocarboxamides can be prepared by reacting acyl glyoxals, isocyanides and carboxylic acids. In order to evaluate the potential of this synthetic method for the preparation of oxazole derivatives, we attempted the synthesis of *N*-substituted 2-alkyl-4-aryloxazole-5-carboxamides (**5**).

The first step of this synthesis consisted in the Passerini reaction between arylglyoxal (**1**), aliphatic carboxylic acids (**2**) and isocyanides (**3**) which afforded *N*-substituted 2-acyloxy-3-oxoarylpropionamides (**4**). Since treatment of compounds **4** with ammonium formate in boiling acetic acid

gave large amounts of by-products, we found that satisfactory yields of **5** were obtained by performing the cyclization of compounds **4** at 100° for 3 hrs. Since a variety of *N*-substituted 2-acyloxy-3-oxocarboxamides can be prepared by changing the arylglyoxal, the isocyanide, and the carboxylic acid, the present method appears to be useful for the synthesis of a great number of *N*,2,4-trisubstituted oxazole-5-carboxamides and, in addition, for all the derivatives obtainable by transformation of the amide group.



1 a Ar = C_6H_5
b Ar = 4-$CH_3C_6H_4$
c Ar = 4-ClC_6H_4

2 a R = CH_3
b R = $C_6H_5CH_2$
c R = 4-$CH_3C_6H_4CH_2$
d R = 4-$NO_2C_6H_4CH_2$

3 a R' = c-C_6H_{11}
b R' = c-C_7H_{13}

4,5 e	Ar = C_6H_5	R = CH_3	R' = c-C_7H_{13}
f	Ar = C_6H_5	R = $C_6H_5CH_2$	R' = c-C_7H_{13}
g	Ar = C_6H_5	R = 4-$CH_3C_6H_4CH_2$	R' = c-C_7H_{13}
h	Ar = C_6H_5	R = 4-$NO_2C_6H_4CH_2$	R' = c-C_7H_{13}
i	Ar = 4-$CH_3C_6H_4$	R = CH_3	R' = c-C_6H_{11}
j	Ar = 4-$CH_3C_6H_4$	R = 4-$CH_3C_6H_4CH_2$	R' = c-C_6H_{11}
k	Ar = 4-ClC_6H_4	R = CH_3	R' = c-C_7H_{13}
l	Ar = 4-ClC_6H_4	R = $C_6H_5CH_2$	R' = c-C_7H_{13}

EXPERIMENTAL SECTION

Melting points were obtained in open capillary tubes and are uncorrected. The IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer for KBr discs. The ^1H NMR spectra were recorded with a Varian Gemini 200 for $CDCl_3$ solutions, chemical shifts are reported in ppm (δ) from TMS.

***N*-Substituted 2-Acyloxy-3-oxocarboxamides (4e-l).**- The appropriate isocyanide (30 mmol) in ether (6 ml) was added to a solution of the arylglyoxal (30 mmol) and the carboxylic acid (45 mmol) in ether (20 ml). When the exothermic reaction had subsided the reaction mixture was allowed to stand for 6 hrs. The solid product that separated out was collected, washed with a little ether, and dried to give **4**. Analytical samples were obtained by recrystallization of the crude prod-

ucts from ethanol.

4e: mp. 114-115°; 65% yield; IR: 3251, 1764, 1707, 1643 cm^{-1}

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.42. Found: C, 68.01; H, 7.25; N, 4.45

4f: mp. 126-127°; 78% yield; IR: 3253, 1753, 1706, 1643 cm^{-1}.

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.15; H, 6.77; N, 3.61

4g: mp. 136-137°; 80% yield; IR: 3260, 1752, 1704, 1643 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.78; H, 7.09; N, 3.64

4h: mp. 122-123°; 85% yield; IR: 3247, 1751, 1702, 1644, 1349 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.81; H, 5.79; N, 6.44

4i: mp. 117-118°; 70% yield; IR: 3270, 1754, 1703, 1644 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.42. Found: C, 68.19; H, 7.19; N, 4.59

4j: mp. 131-132°; 77% yield; IR: 3257, 1754, 1695, 1645 cm^{-1}.

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.79; H, 7.30; N, 3.29

4k: mp. 169-170°; 73% yield; IR: 3264, 1755, 1708, 1643 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}ClNO_4$: C, 61.45; H, 6.30; N, 3.98. Found: C, 61.30; H, 6.46; N, 4.16

4l: mp. 102-103°; 84% yield; IR: 3265, 1751, 1709, 1643 cm^{-1}.

Anal. Calcd for $C_{24}H_{26}ClNO_4$: C, 67.37; H, 6.13; N, 3.28. Found: C, 67.44; H, 6.23; N, 3.02

***N*,2,4-Trisubstituted oxazole-5-carboxamides (5e-l).**- A mixture of **4** (5 mmol), ammonium formate (6.00 g, 95 mmol) and acetic acid (20 ml) was heated at 100° for 3 hrs and then evaporated to dryness. The residue was neutralized with 5% Na_2CO_3 and stirred with water (25 ml) and chloroform (50 ml). The organic layer was separated, dried with Na_2SO_4, and evaporated to dryness. The residue was recrystallized from ethanol to give pure **5**.

5e: mp. 110-111°; 40% yield; IR: 3344, 1634 cm^{-1}; ^1H NMR: δ 6.20 (d, 1H, NH, J = 7.9 Hz), 4.11 (m, 1H, H-1 of cycloheptyl), 2.52 (s, 3H, CH_3).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.55; H, 7.49; N, 9.47

5f: mp. 125-127°; 38% yield; IR: 3259, 1683 cm^{-1}; ^1H NMR: δ 6.08 (d, 1H, NH, J = 7.9 Hz), 4.20 (s, 2H, CH_2), 4.04 (m, 1H, H-1 of cycloheptyl).

Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.90; H, 7.10; N, 7.69

5g: mp. 104-105°; 47% yield; IR: 3333, 1636 cm^{-1}; ^1H NMR: δ 6.12 (d, 1H, NH, J = 7.9 Hz), 4.13 (s, 2H, CH_2), 4.01 (m, 1H, H-1 of cycloheptyl), 2.31 (s, 3H, CH_3).

Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 77.22; H, 7.41; N, 7.37

5h: mp. 140-141°; 42% yield; IR: 3258, 1635 cm^{-1}; ^1H NMR: δ 6.10 (d, 1H, NH, J = 7.9 Hz), 4.27 (s, 2H, CH_2), 4.02 (m, 1H, H-1 of cycloheptyl).

Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.60; H, 6.19; N, 10.20

5i: mp. 167-168°; 50% yield; IR: 3304, 1632 cm^{-1}; ^1H NMR: δ 6.13 (d, 1H, NH, J = 7.7 Hz), 3.97 (m, 1H, H-1 of cyclohexyl), 2.54 (s, 3H, CH_3 oxazole), 2.37 (s, 3H, CH_3 toluene).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.29; H, 7.40; N, 9.52

5j: mp. 144-145°; 45% yield; IR: 3325, 1635 cm^{-1}; ^1H NMR: δ 6.04 (d, 1H, NH, J = 7.7 Hz), 4.11 (s,

2H, CH_2), 3.88 (m, 1H, H-1 of cyclohexyl), 2.32 (s, 3H, $CH_2C_6H_4CH_3$), 2.27 (s, 3H, $C_6H_4CH_3$).
Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 77.48; H, 7.20; N, 7.12
5k: mp. 155-156°; 53% yield; IR: 3314, 1631 cm^{-1}; ^1H NMR: δ 6.23 (d, 1H, NH, J = 7.9 Hz), 4.10 (m, 1H, H-1 of cyclohexyl), 2.53 (s, 3H, CH_3).
Anal. Calcd. for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.42. Found: C, 64.83; H, 6.48; N, 8.46
5l: mp. 142-143°; 54% yield; IR: 3325, 1632 cm^{-1}; ^1H NMR: δ 6.18 (d, 1H, NH, J = 7.9 Hz), 4.18 (s, 2H, CH_2), 4.04 (m, 1H, H-1 of cyclohexyl).
Anal. Calcd for $C_{24}H_{25}ClN_2O_2$: C, 70.50; H, 6.16; N, 6.85. Found: C, 70.41; H, 6.29; N, 6.99

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A ONE-POT SYNTHESIS OF N^{α}-BENZYLOXYCARBONYL-N^{ω}-*t*-BUTOXYCARBONYL-L-ORNITHINE AND L-LYSINE

Submitted by (02/03/92) Elzbieta Masiukiewicz, Barbara Rzeszotarska* and Jaroslaw Szczerbaniewicz

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The title compounds Z-Orn(Boc)[1] and Z-Lys(Boc) serve as valuable intermediates in Schwyzer's strategy of peptide chain assembly using the benzyloxycarbonyl group for temporary protection of α-amino functions and the *t*-butyl type group for permanent protection of side-chain