A New Synthesis of Functionalized 2-Alkylidenetetrahydro-5-furanones by Tandem Alkylation and Translactonization Reactions of 5(4*H*)-Oxazolones

Roberta Cannella,† Francesca Clerici,† Maria L. Gelmi,*,† Michele Penso,‡ and Donato Pocar†

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano, Via Venezian 21, I-20133 Milano, Italy and Centro C.N.R.-C.S.S.S. Speciali Sistemi Organici, Via Golgi 19, I-20133 Milano, Italy

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In recent years significant attention has been focused on the synthesis of derivatives of 2-methylidene- and 2-(halomethylidene)tetrahydro-5-furanones.[1] The biological interest in these classes of compounds is linked to their use as irreversible or reversible inhibitors of the serine proteases (*e.g.* α-chymotrypsin).[2]

Though several preparations of five-membered enol lactones are known,[3] few examples of 3-acylamino derivatives, which incorporate the structure and functionality of α-amino acids, are reported.[1a,4] The lack of general methodologies to prepare 3-acylamino-substituted enol lactones **3** prompted us to develop an efficient synthetic route for these compounds, which rests on tandem alkylation and translactonization reaction of oxazolones **1**.

Synthetically useful procedures for alkylation of oxazolones have been reported. In previous papers[5] we described the C-4 alkylation or arylation of 2,4-disubstituted 5(4*H*)-oxazolones under liquid−liquid phase transfer catalysis (LL-PTC) conditions. Coupling of the alkylation step with an intramolecular nucleophilic attack on the lactone group has been already exploited for the synthesis of heterocyclic compounds, *e.g.* pyrazolone derivatives.[5c]

In a typical procedure, oxazolones **1a**−**c** were made to react with α-halo ketones **2a**−**f** in CH_2Cl_2, using 5% aqueous potassium hydrogen carbonate as base and a catalytic amount of tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) as phase transfer agent. The reactions were completed in 2 h at room temperature (Schemes 1 and 2), and the products **3a**−**i** were isolated in 30−60% yield. Alkylation at C-4 of the oxazolone substrate occurs firstly and the formation of the final product **3** occurs by a translactonization reaction of the intermediate enolate which cannot be isolated under the reaction conditions adopted.

Several α-halo ketones **2** were used and their reactivity was evaluated with regard to the type of halogen, electron-withdrawing group, and alkyl substituents pattern. The reaction of **1a** with ethyl 4-bromo-3-oxobutyrate (**2a**) afforded the enol lactone **3a** in 60% yield, but the yield was decreased to 10% by performing the reaction with the less reactive 4-chloro ketone **2b**. Three different electron-withdrawing groups on the substituted halo ketone, *i.e.* methyl (ethyl) carboxylate, cyano, and nitro groups, were considered. 5(4*H*)-Oxazolones **1** are relatively highly acidic compounds and are easily deprotonated even by relatively weak bases.[6] The resulting anion is readily alkylated by the bromo ketones **2a**,**c**−**f** to give **3a**−**i**. However, alkylation of the anion by 3-bromo-2-oxonitropropane was unsuccessful, presumably due to the competing deprotonation of the halo ketone.

As shown, the reaction is applicable to primary (**2a**−**c**) or secondary acyclic halo ketones (**2d**) (Scheme 1) and to cyclic halo ketones (**2e**,**f**) (Scheme 2). The use of the secondary bromo ketones **2d**−**f** could produce two diastereoisomeric enol lactones. Starting from ethyl 4-bromo-2-methyl-3-oxopentanoate (**2d**) only the isomer **3e** was formed. By contrast, a mixture of the two possible diastereoisomers **3f**,**g** and **3h**,**i** in 3:1 ratio from methyl 3-bromo-2-oxocyclohexanecarboxylate (**2e**) and from 3-bromo-2-oxocyclohexanecarbonitrile (**2f**), respectively (Scheme 2), were obtained.

A comparison between LL-PTC and classical conditions[7] according to Scheme 3 was made by reacting **1a** with **2a**. In the homogeneous system the lactone **3a** was obtained in low yields (27%), whereas the same reaction carried out in PTC conditions afforded compound **3a** in 60% yield, thus verifying the effectiveness of the latter methodology. However, a different behavior was found for 2-phenyl-4-isopropyl-5(4*H*)-oxazolone (**1d**). Reaction with ethyl 4-bromo-3-oxobutyrate (**2a**) did not result in the formation of the expected enol lactone **3l** when performed under PTC conditions. This result is not surprising because it is well known[8] that 4-alkyl-substituted oxazolones, like substrate **1d**, are less resistant toward hydrolysis than 4-arylated derivatives. A low yield (18%) of enol lactone **3l** was obtained by using anhydrous conditions, *i.e.* in THF with ethyldiisopropylamine as deprotonating reactant[7] (Scheme 3).

The translactonization reaction is highly stereoselective and only the *E* enol lactones are produced, as indicated by the chemical shifts of the vinylic protons[9] and by NOESY experiments in which no Overhauser effects between CH and CH_2 protons were observed. Moreover, no evidences for the *Z* isomers were found by ^{1}H NMR analyses of the crude reaction mixtures.

In compound **3e** the 3*S**,4*R** stereochemistry of the two chiral centers was assigned through a NOESY experiment in which the close spatial proximity of Me-3 and NH was demonstrated. The low field shift of H-3 (4.3 δ) and the high field shift of Me-3 (0.85 δ) are both explained by deshielding and shielding effects, respectively, of the substituents on C-5. As above mentioned, the reaction of cyclic ketones afforded two diastereoisomers **3f**,**h** and **3g**,**i**, respectively, whose configurations

† Università di Milano.

‡ Centro C.N.R.

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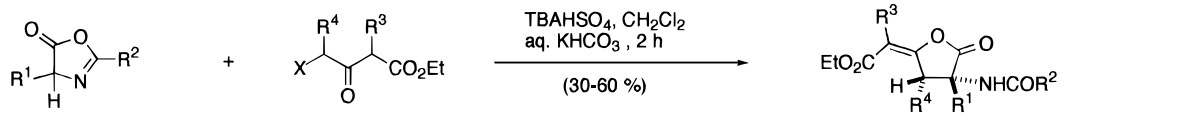
Scheme 1

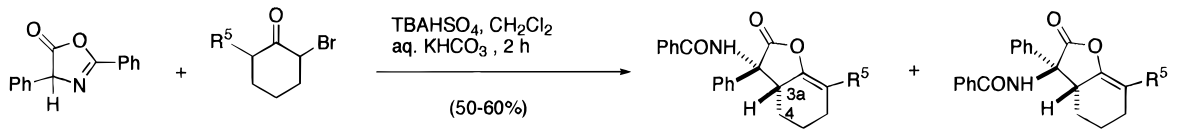


1a: $R^1 = R^2 =$ Ph
1b: R^1 = Ph, R^2 = Ph-4-OMe
1c: $R^1 = CH_2Ph$, R^2 = Ph

2a: X = Br, $R^3 = R^4 = H$
2b: X = Cl, $R^3 = R^4 = H$
2c: X = Br, R^3 = Et, $R^4 = H$
2d: X = Br, $R^3 = R^4$ = Me

3a: $R^1 = R^2$ = Ph, $R^3 = R^4 = H$
3b: R^1 = Ph, R^2 = Ph-4-OMe, $R^3 = R^4 = H$
3c: $R^1 = CH_2Ph$, R^2 = Ph, $R^3 = R^4 = H$
3d: $R^1 = R^2$ = Ph, R^3 = Et, $R^4 = H$
3e: $R^1 = R^2$ = Ph, $R^3 = R^4$ = Me

Scheme 2



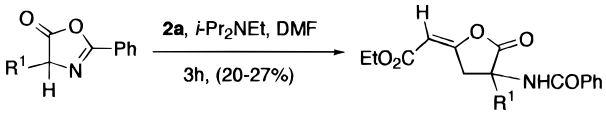
1a

2e: $R^5 = CO_2Me$
2f: R^5 = CN

3f: $R^5 = CO_2Me$
3h: R^5 = CN

3g: $R^5 = CO_2Me$
3l: R^5 = CN

Scheme 3



1a: R^1 = Ph
1d: R^1 = *i*-Pr

3a: R^1 = Ph
3l: R^1 = *i*-Pr

are assigned on spectroscopic grounds (^{1}H NMR). The ^{1}H NMR spectral assignments of the protons of each isomer were made by several two-dimensional experiments. In particular, homonuclear COSY was employed to assign the chemical shift of the CH and CH_2 groups because the NOESY spectra did not give sufficient information about the spatial proximity of H-3*a* and NH groups. The signals associated with protons of isomers **3g**,**i** are all in the expected range,[10] while in isomers **3f**,**h** H-3*a* is deshielded (4.30−4.15 δ) and one of H-4 shows an unusually high shielding (0.80−0.55 δ), indicating that neighboring substituent effects similar to those which exist in the ^{1}H NMR spectrum of compound **3e** are operating in this case, too. This is confirmed by molecular model inspection. Accordingly the 3*R**,3*aR** and 3*S**,3*aR** configurations are associated with **3f**,**h** and **3g**,**i**, respectively.

In conclusion, we have described an efficient synthetic route to prepare enol lactones **3**,[11] that are analogues of phenylglycine and phenylalanine, in a single step and by use of readily available materials (*i.e.* oxazolones **1** and α-bromo ketones **2** functionalized in the α′-position with an electron-withdrawing group). The reaction proceeds with good stereoselectivity at the exocyclic double bond, and different substitution patterns are possible.

Experimental Section

Chloro ketone **2b** is a commercial product, and bromo ketones **2a**,**c**−**f** were obtained following published procedures.[12]

General Procedure for the Preparation of 2-Alkylidenetetrahydro-5-furanones 3. Method A. A solution of oxazolone **1a**−**c** (2.5 mmol), ketone **2** (2.5 mmol), and $TBAHSO_4$ (0.25 mmol) in CH_2Cl_2 (6 mL) was vigorously stirred at room temperature. An aqueous 5% $KHCO_3$ solution (2.76 mmol) was added dropwise in 2 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The dichloromethane extracts were washed with water until neutral to litmus, dried (Na_2SO_4), and evaporated. The residue was chromatographed, and compound **3** was further purified by crystallisation. Yields and analytical data are reported in Table 1.

Table 1. Column Chromatography Conditions and Yields for Compounds 3

compd	CC eluant (ratio)[a]	yield (%)	mp (°C) (solvent)
3a	A (1:19)	60	159 (Et_2O)
3b	A (1:19)	45	159 (CH_2Cl_2−C_6H_{12})
3c	A (1:19)	37	159 (Et_2O)
3d	A (1:19)	30	135 (CH_2Cl_2−C_6H_{12})
3e	A (1:19)	50	146 (CH_2Cl_2−C_6H_{12})
3f	B (1:0 to 0:1)	48	120 (CH_2Cl_2−C_6H_{12})
3g	B (1:0 to 0:1)	16	180 (CH_2Cl_2−C_6H_{12})
3h	B (1:0 to 0:1)	34	119 (CH_2Cl_2−C_6H_{12})
3i	B (1:0 to 0:1)	14	175 (CH_2Cl_2−C_6H_{12})
3l	C (1:4)	18	139 (Et_2O)

[a] Column chromatography (CC) eluant: A: AcOEt−toluene; B: *n*-pentane−Et_2O; C: AcOEt−cyclohexane.

Method B. A solution of oxazolone **1a**,**d** (4.2 mmol), ketone **2a** (4.2 mmol), and *i*-Pr_2NEt (7.2 mmol) in anhydrous DMF (6 mL) was stirred at room temperature under nitrogen for 3 h. The solvent was evaporated *in vacuo* (T < 40 °C), and the crude reaction mixture was chromatographed. Compound **3** was isolated after recrystallization (**3a**: 27%; **3l**: 18%).

Ethyl (*E*)-[4-(Benzoylamino)-5-oxo-4-phenyl-dihydrofuran-2-ylidene]acetate (3a): IR ν_{max} 3305, 1815, 1710, 1665 cm^{-1}; ^{1}H NMR δ 7.81−7.26 (m, 10 H), 6.76 (s, 1 H, D_2O-ex), 5.78, 4.26, 4.06 (ABX system, J_{AB} = 18.7 Hz, J_{AX} = 2.6 Hz, J_{BX} = 1.6 Hz, 3 H), 4.26−4.11 (m, 2 H), 1.29 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 39.4, 60.4, 61.7 (C-3), 98.2 (=CH), 125.9−132.7, 164.0, 166.6, 167.2, 171.5.

Ethyl (*E*)-[4-[(4-Methoxybenzoyl)amino]-5-oxo-4-phenyl-dihydrofuran-2-ylidene]acetate (3b): IR ν_{max} 3270, 1820, 1710, 1660 cm^{-1}; ^{1}H NMR δ 7.70−6.90 (m, 9 H), 6.68 (s, 1 H, D_2O-ex), 5.77, 4.23, 4.04 (ABX system, J_{AB} = 18.8 Hz, J_{AX} = 2.6 Hz, J_{BX} = 1.6 Hz, 3 H), 4.26−4.11 (m, 2 H), 3.85 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H).

Ethyl (*E*)-[4-(Benzoylamino)-4-benzyl-5-oxo-dihydrofuran-2-ylidene]acetate (3c): IR ν_{max} 3300, 1810, 1705, 1660 cm^{-1}; ^{1}H NMR δ 7.81−7.26 (m, 10 H), 6.60 (s, 1 H, D_2O-ex), 5.55, 3.86, 3.56 (ABX system, J_{AB} = 19.1 Hz, J_{AX} = 2.5 Hz, J_{BX} = 1.7 Hz, 3 H), 4.20−4.09 (m, 2 H), 3.26, 3.19 (dd, J_{AB} = 21.6 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H).

Ethyl (*E*)-2-[4-(Benzoylamino)-5-oxo-4-phenyl-dihydrofuran-2-ylidene]butyrate (3d): IR ν_{max} 3305, 1805, 1700, 1645

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(11) Enzymatic studies with lactones **1** will be described elsewhere.
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cm^{-1}; ^1H NMR δ 7.80−7.40 (m, 10 H), 6.70 (s, 1 H, D_2O-ex), 4.28−4.16 (m, 2 H), 4.23, 4.01 (AB system, $J_{AB} = 18.6$ Hz, 2 H), 2.45 (q, $J = 7.0$ Hz, 2 H), 1.30 (t, $J = 7.0$ Hz, 3 H), 1.05 (t, $J = 7.4$ Hz, 3 H).

Ethyl (3*S,4*R**)-(*E*)-2-[4-(Benzoylamino)-3-methyl-5-oxo-4-phenyl-dihydrofuran-2-ylidene]propionate (3e):** IR ν_{max} 3305, 1815, 1705, 1640 cm^{-1}; ^1H NMR δ 7.80−7.26 (m, 10 H), 6.83 (s, 1 H, D_2O-ex), 4.31 (q, $J = 7.3$ Hz, 1 H), 4.26−4.11 (m, 2 H), 2.05 (s, 3 H), 1.29 (t, $J = 7.0$ Hz, 3 H), 0.85 (d, $J = 7.3$ Hz, 3 H).

Methyl (3*R,3*aR**)-3-(Benzoylamino)-2-oxo-3-phenyl-2,3,3*a*,4,5,6-hexahydro-benzofuran-7-carboxylate (3f):** IR ν_{max} 3280, 1805, 1720, 1680 cm^{-1}; ^1H NMR δ 7.90−7.20 (m, 10 H), 6.80 (s, 1 H, D_2O-ex), 4.30−4.15 (m, 1 H, H-3*a*), 3.80 (s, 3 H), 2.50−2.35 (m, 1 H, H-6), 2.27−2.10 (m, 1 H, H-6), 2.10−1.95 (m, 1 H, H-4), 1.90−1.80 (m, 1 H, H-5), 1.70−1.50 (m, 1 H, H-5), 0.80−0.55 (m, 1 H, H-4).

Methyl (3*S,3*aR**)-3-(Benzoylamino)-2-oxo-3-phenyl-2,3,3*a*,4,5,6-hexahydro-benzofuran-7-carboxylate (3g):** IR ν_{max} 3285, 1815, 1680, 1660 cm^{-1}; ^1H NMR δ 7.80−7.38 (m, 10 H), 6.50 (s, 1 H, D_2O-ex), 3.80 (s, 3 H), 3.48−3.31 (m, 1 H, H-3*a*), 2.58−2.45 (m, 2 H, H-4), 2.20−1.95 (m, 2 H, H-5, H-6), 1.80-1.60 (m, 2 H, H-6, H-5).

(3*R,3*aR**)-*N*-(7-Cyano-2-oxo-3-phenyl-2,3,3*a*,4,5,6-hexahydrobenzofuran-3-yl)benzamide (3h):** IR ν_{max} 3320, 2205, 1820, 1680 cm^{-1}; ^1H NMR δ 7.85−7.15 (m, 10 H), 6.75 (s, 1 H, D_2O-ex), 4.30−4.15 (m, 1 H, H-3*a*), 2.36−2.23 (m, 1 H, H-6), 2.15−2.00 (m, 1 H, H-6), 2.00−1.87 (m, 1 H, H-4), 1.85−1.75 (m, 1 H, H-5), 1.60−1.40 (m, 1 H, H-5), 0.70−0.55 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.4, 23.4, 24.6 (CH_2), 45.1 (C-3*a*), 67.5 (C-3), 87.4 (C-7), 125.6 (CN), 132.8−133.8, 160.9, 168.1, 171.1.

(3*S,3*aR**)-*N*-(7-Cyano-2-oxo-3-phenyl-2,3,3*a*,4,5,6-hexahydrobenzofuran-3-yl)benzamide (3i):** IR ν_{max} 3320, 2190, 1805, 1660 cm^{-1}; ^1H NMR δ 7.80−7.32 (m, 10 H), 6.55 (s, 1 H, D_2O-ex), 3.35−3.22 (m, 1 H, H-3*a*), 2.40−2.28 (m, 2 H, H-4), 2.20−2.18 (m, 1 H, H-6), 2.20−1.90 (m, 1 H, H-5), 1.70−1.50 (m, 2 H, H-6, H-5); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.7 (CH_2), 46.2 (C-3*a*), 68.3 (C-3), 83.7 (C-7), 115.7 (CN), 132.8-133.82, 162.5, 168.1, 170.9.

Ethyl (*E*)-[4-(Benzoylamino)-4-isopropyl-5-oxo-dihydrofuran-2-ylidene]acetate (3l): IR ν_{max} 3290, 1825, 1700, 1650 cm^{-1}; ^1H NMR δ 7.70−7.40 (m, 5 H), 6.50 (s, 1 H, D_2O-ex), 5.76, 3.57, 3.53 (ABX system, $J_{AB} = 19.5$ Hz, $J_{AX} = 2.4$ Hz, $J_{BX} = 1.9$ Hz, 3 H), 4.30−4.11 (m, 2 H), 2.29−2.23 (m, 1 H), 1.28 (t, $J = 7.1$ Hz, 3 H), 1.15, 0.99 (td, 6 H).

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