One-Pot Synthesis of α-Alkylidene-γ-butyrolacton-2-ones (Tetronic Acid Derivatives): Polar Solvent Induces a New Type of γ-Lactonization

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Abstract: An efficient, one-pot synthetic protocol toward α-alkylidene-γ-butyrolacton-2-ones, a rather unexplored class of heterocyclic scaffolds starting from primary amines, methyl acetoacetate, and chloroacetyl chloride is described. The mixture of MeCN–MeOH as a polar solvent triggers a new cycloaddition of the enaminone intermediate. The reaction is completed within 12 hours under reflux condition to produce the title compounds.

Key words: γ-lactone, α-alkylidene-γ-butyrolactone, tetronic acid, enaminone, chloroacetyl chloride, polar solvent, one-pot multicomponent reaction

Lactones of five, and larger rings, are of interest because of their applications in building up biologically active compounds, which exhibit various pharmacological activities.[1–5] They are commonly known for their cytostatic and antimicrobial[6,7] activity. Many of them have feeding deterrent activity against insects.[8–10] Interest in naturally occurring and synthetic α-alkylidene-γ-butyrolactones is surging[11] as several of them have been shown to display anti-inflammatory COX-2 inhibition, as well as phytotoxic and cytotoxic activities.[12] The α-alkylidene-γ-butyrolactone substructure has attracted particular attention, not only for being present in a wide range of biologically active natural products[13] [for example, galanolactone (**1**), Figure 1], but also as starting materials in various synthetic transformations. They can undergo reduction,[14] oxidation,[15] aziridination,[16] 1,3-dipolar,[17] and Diels–Alder[18] cycloadditions, nucleophilic conjugate additions,[18] and intramolecular Stetter reactions.[19]

Tetronic acid derivatives and their metabolites are widespread in nature, whereof vitamin C and penicillic acid are undoubtedly the most important.[20] A large array of biological properties including antibutic, analgesic, insecticidal, antifungal, and antitumor properties[21] have attracted the interest of many research groups on the synthesis of this class of heterocyclic compounds. Recently ester derivatives of nodulisporacid A (**2**) isolated from a marine-derived fungus *Nodulisporium sp*. CRIF1 have been found to show activity against eleven cancer cell lines.[22]

On account of this wide range of activity, a variety of synthetic methods for both tetronic acids[23] and α-alkylidene-γ-butyrolactones[24] has been developed. Surprisingly, to our knowledge, there currently exists no efficient procedure for the synthesis of compounds including a combination of these two characteristic substructures together directly from readily available building blocks.

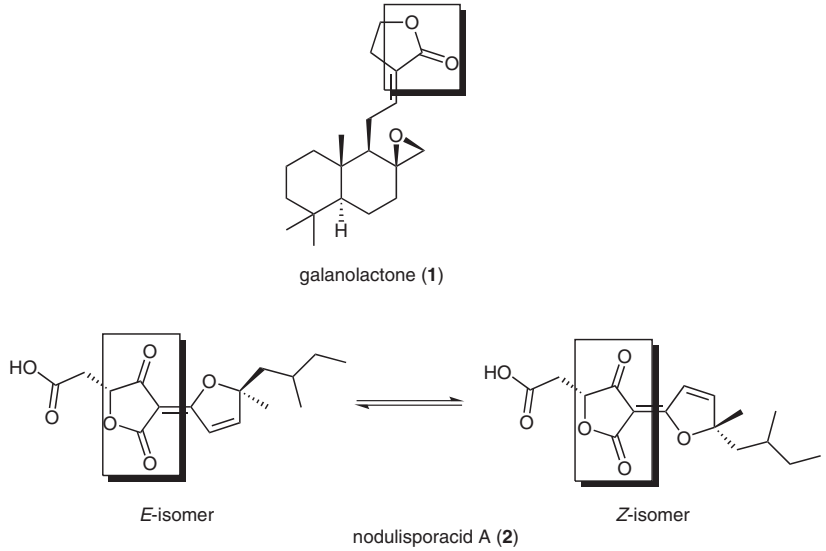

Figure 1 Natural products, which contain the α-alkylidene-γ-butyrolactone substructure

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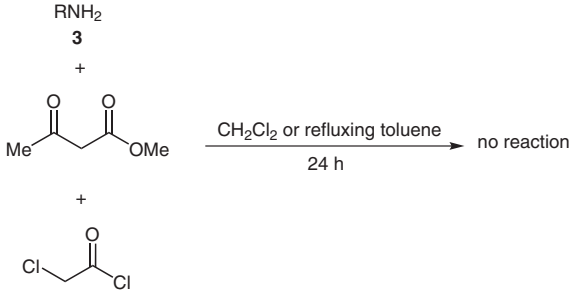
Recently, our group reported the synthesis of a novel series of heterocyclic compounds using the reaction of enamines or enaminones with various electrophiles via one-pot MCR.[25] In a continuation of this study, we become interested in the application of chloroacetyl chloride (which display electrophilic property at two sites of its structure) via multicomponent reaction for synthesis of α-alkylidene-γ-butyrolacton-2-ones as tetronic acid analogues. Our strategy to reach this goal is outlined in Table 1. Reaction between primary amines **3**, methyl acetoacetate, and chloroacetyl chloride in a mixture of MeCN–MeOH as solvent under thermal conditions leads to the formation of [1-(alkylamino)ethylidene]-2,4(3*H*,5*H*)-furandione **4** after 12 hours in 70–85% yields.[26]

To show the effect of polar solvent, the reaction of primary amine **3**, methyl acetoacetate, and chloroacetyl chloride was performed in CH_2Cl_2 or refluxing toluene. After 24 hours, the ^1H NMR spectrum of the reaction mixture showed that product **4** has been not formed even in a trace amount (Scheme 1).

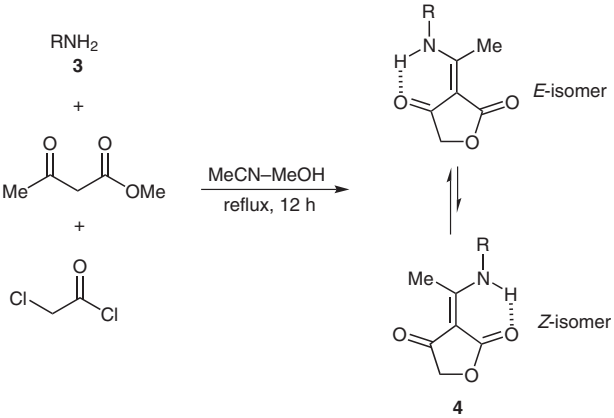


Scheme 1 The reaction in CH_2Cl_2 or refluxing toluene

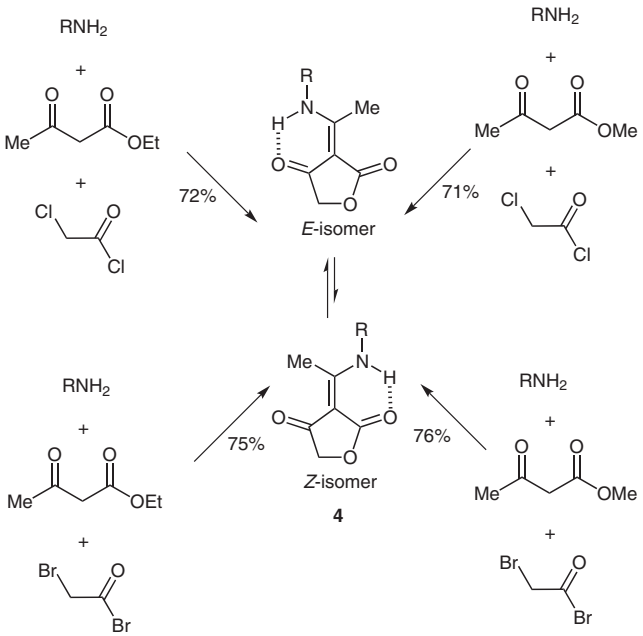
To investigate the scope and limitations of the reaction, and especially to confirm the proposed product structure **4**, we first decided to study the effect of using different alkyl acetoacatate (ethyl acetoacatate) and performed its reaction with primary amine **3** and chloroacetyl chloride under the same conditions. It was found that the reaction was quite general towards the alkyl acetoacatate component. In view of the success of the reaction, we then employed bromoacetyl bromide under these conditions to form the [1-(alkylamino)ethylidene]-2,4(3*H*,5*H*)-furandiones **4**, with slightly increased yield. All of our results were summarized in Scheme 2.

The structures of compounds **4a–h** were deduced from their, mass, IR, and high field ^1H NMR and ^{13}C NMR spectra as described for **4a**. The mass spectrum of **4a** displayed a molecular ion peak at *m/z* = 169. Initial fragmentation for most products involved the loss of H_2O with **4a** showing a fragment ion at *m/z* = 151. In the IR spectrum of **4a**, one absorption band at 3460, three bands at 1728, 1638, and 1615 cm^{-1}, which are, respectively, related to NH, C=O of ketone, C=O of ester, and C=C stretching frequencies, clearly indicated the most important functional groups of the product.

Table 1 Reaction between Primary Amines **3**, Methyl Acetoacetate and Chloroacetyl Chloride in a Mixture of MeCN–MeOH as Solvent under Thermal Conditions

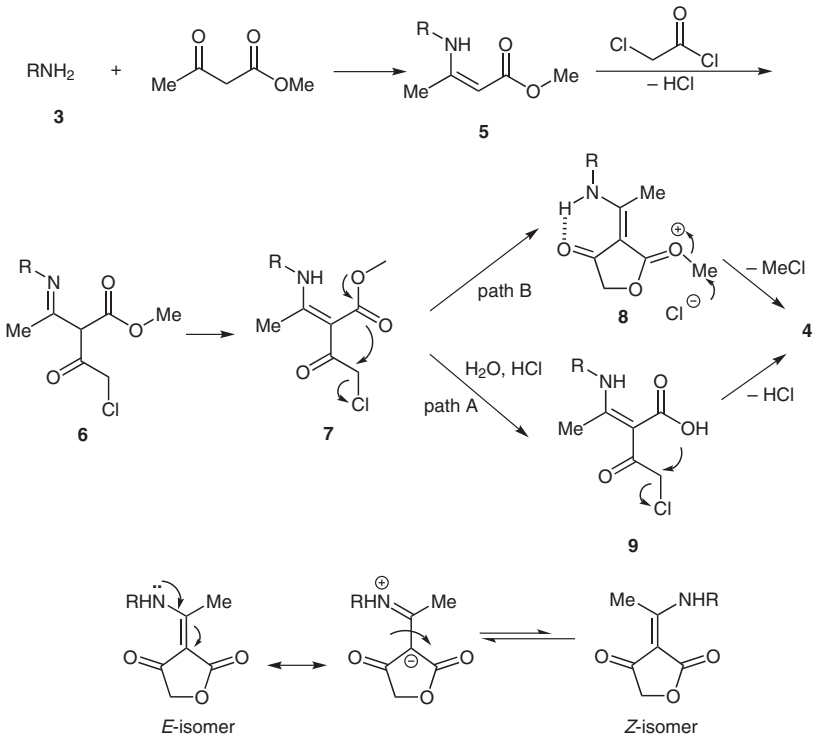


Entry	R	Yield of **4** (%)	*E*/*Z*
1	Et	**4a** 71	53:47
2	*n*-Pr	**4b** 80	66:34
3	*n*-Bu	**4c** 75	60:40
4	*t*-Bu	**4d** 77	62:38
5	*i*-Pr	**4e** 82	67:33
7	*i*-Bu	**4f** 70	60:40
8	All	**4g** 78	63:37
9	Cy	**4h** 85	63:37



Scheme 2 Evaluation of ethyl acetoacatate and bromoacetyl bromide in the reaction under similar conditions. Conditions for all reactions: MeCN–MeOH, reflux, 12 h.

The presence of these two rotational isomers was confirmed by the ^1H NMR and ^{13}C NMR spectra of **4a–h**



Scheme 3 The proposed mechanism for the formation of α-alkylidene-γ-butyrolacton-2-one (tetronic acid) **4**

where two sets of peaks were detected. The ^{1}H NMR spectrum of **4a** exhibited two triplet signals at 1.32 ($^3J_{HH}$ = 7.3 Hz) and 1.35 ppm ($^3J_{HH}$ = 7.3 Hz) readily recognized as arising from two CH_2CH_3 groups. Two sharp singlet signals at δ = 2.54 and 2.58 ppm are related to two methyl groups. Two quartets at δ = 3.47 and 3.50 ppm ($^3J_{HH}$ = 7.3 Hz for both of them) correspond to the two CH_2CH_3 groups. The CH_2 of the lactone ring appears as two singlet signals at δ = 4.38 and 4.40 ppm. The signal of the NH for the two rotamers appears as two relatively broad signals at δ = 10.01 and 10.99 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** is in agreement with the product structure. In the aliphatic region there are 8 signals related to four Me and four CH_2 groups. Two quaternary carbon of two rotamers which are attached to two C=O groups resonate at δ = 90.36 and 91.76 ppm. The most important region of the spectrum is related to carbonyl groups that have 4 C=O signals for two rotamers.

Although no detailed mechanistic studies have been carried out at this point, a possible reaction sequence leading to the product **4** is depicted in Scheme 3. First, the reaction of primary amine **3** and methyl acetoacetate would provide the enaminone intermediate **5**. Addition of the enaminone **5** to chloroacetyl chloride flowed by loss of HCl gives 2-imino-1,3-dicarbonyl **6** which tautomerizes to enaminone **7**. In path A, in the presence of H_2O and HCl intermediate **7** converts to related carboxylic acid **9**. In path B, the polar solvent induces intramolecular nucleophilic addition of the ester oxygen to the electrophilic carbon attached to Cl and subsequently ion-paired **8** is generated via a SN_2 internal reaction. Finally, the two possible intermediates **8** or **9** provide the observed product **4** by loss of a molecule of MeCl or HCl, respectively.

In conclusion, we have reported a novel and convenient one-pot synthesis of α-alkylidene-γ-lacton-2-ones (tetronic acids). This class of compounds is not only prepared by a multicomponent reaction for the first time but also to our knowledge, there is no other efficient method for their synthesis. As regards the structural viewpoint, these materials are tetronic acids on one hand and α-alkylidene-γ-lactones on the other, as well as possessing an enamine component. Other features of this reaction are that it is performed under neutral, catalyst-free conditions and constitutes a simple and direct high-yield approach to this class of compounds. The simplicity of this procedure makes it an interesting alternative to complex multistep approaches.

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(26) To a magnetically stirred 10 mL flat-bottom flask, containing ethylamine (0.09 g, 2 mmol) was added methyl acetoacetate (0.24 g, 2 mmol), and this mixture was stirred at r.t. under solvent-free conditions for 10 min. A solution of chloroacetyl chloride (0.22 g, 2 mmol) in MeCN (5 mL) was added dropwise to the reaction mixture. The progress of the reaction was followed by TLC. When enaminone **5** was fully consumed, MeOH (2 mL) was added and the mixture allowed to stir at 110–120 °C for 11 h. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc = 1:1) to obtain product **4a** as a white powder (0.12 g, 71%). IR (KBr): 3460 (NH), 1728 (CO_2), 1638 (C=O), 1615 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 169 (93) [M^+], 151 (85), 123 (38), 95 (34), 82 (69), 68 (50), 58 (100), 42 (92).
E-Isomer of **4a**: ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.35 (3 H, t, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3), 2.54 (3 H, s, CH_3), 3.47 (2 H, q, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3), 4.40 (2 H, s, CH_2O), 10.99 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 13.86 (CH_2CH_3), 14.42 (CH_3), 38.43 (CH_2CH_3), 69.97 (OCH_2), 91.76 (C=CCH_3), 170.80 (C=CCH_3), 172.52 (CO_2), 197.10 (C=O).
Z-isomer of **4a**: ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.32 (3 H, t, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3), 2.58 (3 H, s, CH_3), 3.50 (2 H, q, $^3J_{H,H}$ = 7.3 Hz, CH_2CH_3), 4.38 (2 H, s, CH_2O), 10.01 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 14.27 (CH_2CH_3), 14.62 (CH_3), 38.12 (CH_2CH_3), 72.00 (OCH_2), 90.36 (C=CCH_3), 169.94 (C=CCH_3), 176.35 (CO_2), 193.62 (C=O).
Compound **4b**: yield 0.28 g (80%); white powder; mp 112–114 °C. IR (KBr): 3465 (NH), 1734 (CO_2), 1661 (C=O), 1604 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 183 (100) [M^+], 165 (87), 154 (70), 150 (59), 137 (39), 125 (47), 97 (75), 82 (72), 67 (70).
E-isomer of **4b**: ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.05 (3 H, t, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3), 1.75 (2 H, q, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3), 2.55 (3 H, s, CH_3), 3.43 (2 H, t, $^3J_{H,H}$ = 6.9 Hz, CH_2N), 4.42 (2 H, s, OCH_2), 11.10 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 11.16 (CH_2CH_3), 13.96 (CH_3), 30.87 (CH_2CH_3), 45.18 (CH_2N), 69.97 (CH_2O), 91.88 (C=CCH_3), 161.90 (C=CCH_3), 170.96 (CO_2), 197.18 (C=O).
Z-isomer of **4b**: ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.03 (3 H, t, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3), 1.72 (2 H, q, $^3J_{H,H}$ = 7.4 Hz, CH_2CH_3), 2.60 (3 H, s, CH_3), 3.40 (2 H, t, $^3J_{H,H}$ = 7.0 Hz, CH_2N), 4.40 (2 H, s, OCH_2), 10.13 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 11.16 (CH_2CH_3), 14.37 (CH_3), 31.22 (CH_2CH_3), 44.85 (CH_2N), 72.04 (CH_2O), 90.44 (C=CCH_3), 161.93 (C=CCH_3), 170.07 (CO_2), 193.61 (C=O).
Compound **4e**: yield 0.28 g (82%); white powder; mp 118–120 °C. IR (KBr): 3230 (NH), 1725 (CO_2), 1639 (C=O), 1604 (C=C) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 183 (100) [M^+], 165 (78), 137 (24), 110 (39), 96 (94), 83 (47), 67 (35), 55 (16).
E-isomer of **4e**: ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.30 (6 H, d, $^3J_{H,H}$ = 6.2 Hz, 2 $CHCH_3$), 2.51 (3 H, s, CH_3), 3.91–3.99 (1 H, m, 1 $CHCH_3$), 4.33 (2 H, s, CH_2O), 10.94 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 13.85 (2 $CHCH_3$), 22.82 (CH_3), 45.75 ($CHCH_3$), 69.89 (CH_2O),

91.43 (*C*=CCH$_3$), 169.43 (C=*C*CH$_3$), 172.53 (CO_2), 196.96 (C=O).

Z-isomer of **4e**: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.28 (6 H, d, $^3J_{H,H}$ = 6.2 Hz, 2 CHC*H*$_3$), 2.56 (3 H, s, CH_3), 3.91–3.99 (1 H, m, C*H*CH$_3$), 4.30 (2 H, s, CH_2O), 9.94 (1 H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 14.31 (2 CH*C*H$_3$), 22.78 (CH_3), 45.41 (*C*HCH$_3$), 71.84 (CH_2O), 90.05 (*C*=CCH$_3$), 168.61 (C=*C*CH$_3$), 176.31 (CO_2), 193.58 (C=O).