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A concise synthesis of highly functionalized α,β-unsaturated γ-butyrolactones through ring contraction of 2*H*-pyran-2-ones☆

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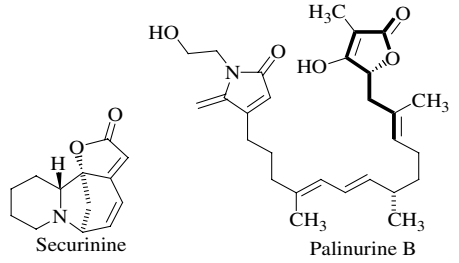
Abstract—2-Oxo-5-(1-arylvinyl)-4-piperidin-1-yl-2,5-dihydrofuran-3-carbonitriles **3** have been synthesized through ring contraction of suitably functionalized 2*H* -pyran-2-ones **1** by a carbanion generated in situ from nitromethane **2** in good yield. In some cases their counterpart tautomers 2-oxo-5-(1-arylethylidene)-4-piperidin-1-yl-2,5-dihydrofuran-3-carbonitriles **4** have also been isolated and characterized as minor products.

α,β-Unsaturated γ-butyrolactones, being integral parts of numerous biologically active natural products[1] such as securinine[2] **I** and palinurine B[3] **II** display diverse pharmacological activities and are considered useful building blocks for the construction of complex natural products and pharmaceuticals of therapeutic importance.



Compounds with the α,β-unsaturated γ-lactone skeleton display a broad range of antibiotic,[4] anti-inflammatory[5] and cytotoxic activities[5] and have aroused considerable interest in developing novel approaches to the synthesis of this class of compound. Among various reported procedures[6,7] in the literature for the synthesis of α,β-unsaturated γ-butyrolactones, Ag or Pd-catalyzed lactonization of suitably substituted (*Z*)-2-en-4-ynoic acids is highly prominent.[7a,8,9] Winterfeldt synthesized[10] compounds with this ring system by triphenylphosphine-catalyzed lactonization from benzaldehyde and dimethyl acetylenedicarboxylate. The process was further modified to improve the yield[11] using activated ketones as the substrate. Silyloxy furans have recently been used as precursors for the synthesis of various 5*H*-furan-2-one derivatives.[12] A new route for the synthesis of 4-pyrrolidin-1-yl-5*H*-furan-2-ones has been developed,[13] which involves the [2,3]-Wittig rearrangement of γ-allyloxy-β-pyrrolidin-1-yl-(*E*)-2-butenoate dienolates followed by cyclization. Recently, the α,β-unsaturated γ-butyrolactone ring system has been prepared[14] by prolonged refluxing of a mixture of pyrylium salts with sodium cyanide.

We report here, an efficient and concise route for the synthesis of α,β-unsaturated γ-butyrolactones by ring contraction of suitably functionalized 2*H*-pyran-2-ones derived from nitromethane in good yield. To the best of our knowledge, this is the first report of the formation of α,β-unsaturated γ-butyrolactones from 2*H*-pyran-2-ones through ring transformation and one, which has superiority over existing procedures in having mild reaction conditions, an easy work-up and no requirement for any catalyst. In fact this study was aimed at synthesizing 2-nitroaniline derivatives from the reaction of suitably functionalized 2*H*-pyran-2-ones with nitromethane.

Keywords: Butyrolactones; Ring contraction; Reaction mechanism.
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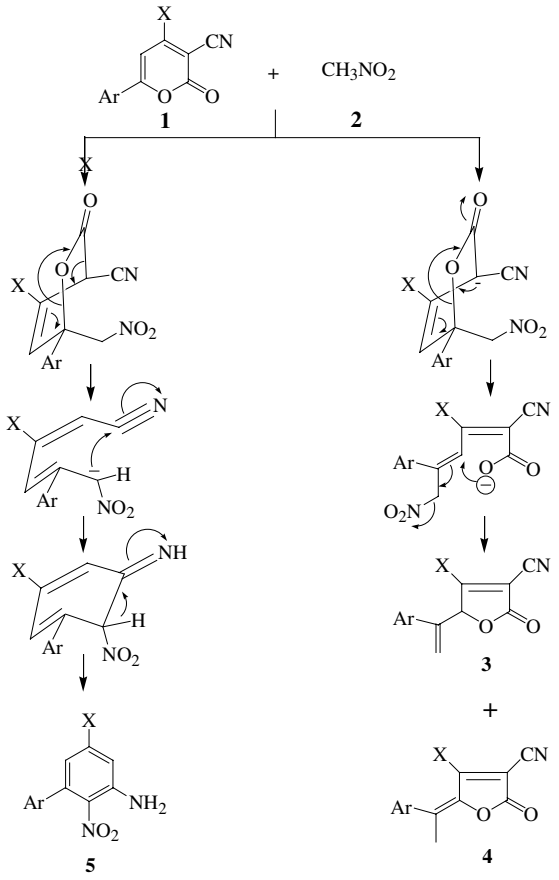
In this reaction we had the impression that the carbanion generated from nitromethane in situ would attack the highly electropositive carbon centre (C6) of the pyran ring followed by decarboxylation and ring closure involving the methylene group and the cyano substituent present at position 3 of the pyran ring. The compounds isolated however were characterized as an α,β-unsaturated γ-butyrolactone **3** and a 2-oxo-5-(1-arylethylidene)-4-substituted-2,5-dihydrofuran-3-carbonitrile **4** instead of the 2-nitroaniline.

In the formation of **3**, the initial step is still the attack of the carbanion from the nitromethane at C6 of the pyran ring followed in this case by ring opening and relactonization, involving the carboxyl group and C5 of the pyran ring with elimination of the nitro group as depicted in Scheme 1. The formation of product **4** may have arisen due to partial isomerization of **3** under the reaction conditions used.

Thus, an equimolar mixture of a 2*H*-pyran-2-one **1** and nitromethane **2** in DMF was stirred in the presence of powdered KOH (1.5 mmol) for 24 h at room temperature and then poured onto crushed ice with vigorous stirring. The cold solution after neutralization with aqueous 10% HCl, liberated a precipitate, which was filtered, washed with water and finally purified on a Si-gel column. The two products isolated were characterized as



Scheme 1. Preparation of γ-butyrolactones **3** and **4**.

Table 1. α,β-Unsaturated γ-butyrolactone derivatives **3a–j** and **4a–j** produced via Scheme 1

3, 4	X	Ar	Yield (%)	
			3	4
a	Pyrrolidin-1-yl	4-Tolyl	75	—
b	Pyrrolidin-1-yl	4-Chlorophenyl	73	—
c	Piperidin-1-yl	Phenyl	65	12
d	Piperidin-1-yl	4-Tolyl	62	14
e	Piperidin-1-yl	4-Methoxyphenyl	61	16
f	Piperidin-1-yl	4-Fluorophenyl	60	—
g	Piperidin-1-yl	4-Chlorophenyl	64	—
h	Piperidin-1-yl	4-Bromophenyl	67	—
i	Piperidin-1-yl	2-Furyl	69	12
j	Piperidin-1-yl	2-Thienyl	75	10

a 2-oxo-5-(1-arylvinyl)-4-substituted-2,5-dihydrofuran-3-carbonitrile **3** as the major product and in some cases, a 2-oxo-5-(1-arylethylidene)-4-piperidin-1-yl-2,5-dihydrofuran-3-carbonitrile **4** as a minor product (Table 1).

The lactones **1** used as precursors were prepared in two steps. The first step was the formation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile from the reaction[15] of methyl 2-cyano-3,3′-dimethylsulfanylacrylate and a ketone. The lactone thus formed was aminated[16] by refluxing with a secondary amine in alcohol, which afforded 6-aryl-4-pyrrolidinyl/piperidinyl-2*H*-pyran-2-one-3-carbonitriles **1** in good yields.

The structures of compounds **3** and **4** were distinguished unambiguously from ^{1}H NMR spectra. The ^{1}H NMR of **3c** showed a singlet at δ 5.41 for a methine proton and at δ 5.60 for the methylene protons, which were missing in **4**. The appearance of a singlet at δ 2.34 in **4** was due to the methyl protons. All the other compounds were characterized[17] by elemental and spectroscopic analyses. The structures of compounds **3c** and **4j** were further confirmed by single-crystal X-ray diffraction study[18] was shown in Figures 1 and 2 with their corresponding atomic numbering schemes. The X-ray molecular structure of **4j** (Fig. 2) shows the *Z*-conformation along the double bond between the C5 and C7 atoms, leading to an almost planar arrangement between the thiophene and the central butyrolactone ring [twisting angle: 8.2 (2)°], whereas in molecule **3c** (Fig. 1), the twisting angle between the least-square mean plane of the butyrolactone and the phenyl ring is 48.6 (1)°, which indicates the rotational freedom due to the presence of a single bond.

Attempts to transform **3** into **4** by heating **3** at its melting point for 1 h failed, thereby proving its thermal stability. In this reaction other bases such as alkoxides and sodium hydride were also tried but none of these were found to be better. A plausible mechanism for this reaction is depicted in Scheme 1.

Thus our methodology provides an easy access to the synthesis of α,β-unsaturated γ-butyrolactones in one step in more than 60% yield. This method is far superior to known literature procedures in terms of ease of work-

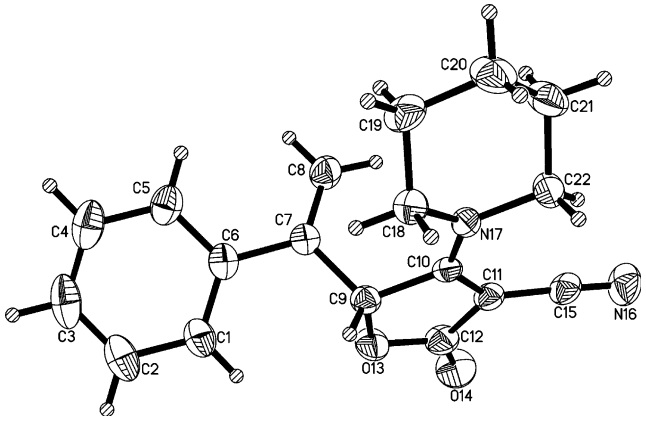


Figure 1. Displacement ellipsoid plot (30% probability) of the X-ray crystal structure of **3c**.

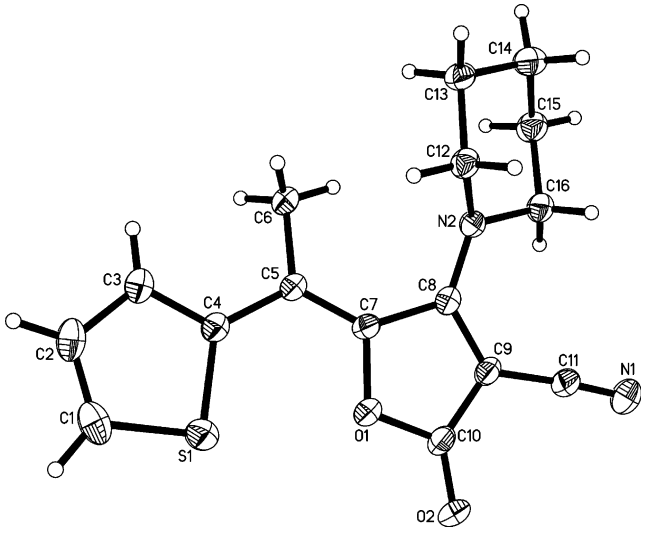


Figure 2. Displacement ellipsoid plot (30% probability) of the X-ray crystal structure of **4j**.

up, use of economic reagents and the possibility of varying substituents in the lactone ring.

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17. Typical procedure: A mixture of 2*H*-pyran-2-one **1** (1 mmol), nitromethane **2** (1 mmol) and powdered KOH (1.5 mmol) in dry DMF (15 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto ice-water and neutralized with 10% HCl. The separated solid was filtered, washed with water and dried. The crude product was purified on a Si-gel column using 1% ethyl acetate in chloroform as eluent. Compound **3d**: mp 138–140 °C, IR (KBr) $\nu = 2207\,cm^{-1}$ (CN), $1748\,cm^{-1}$ (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.69 (b s, 6H, $3CH_2$), 2.37 (s, 3H, CH_3), 3.23–3.25 (m, 2H, NCH_2), 3.91–3.94 (m, 2H, NCH_2), 5.38 (s, 1H, CH), 5.62 (s, 1H, CH_2), 5.65 (s, 1H, CH_2), 7.17–7.21 (d, $J = 8.0$ Hz, 2H, ArH), 7.29–7.33 (d, $J = 8.1$ Hz, 2H, ArH); MS (FAB) 309 (M^++1); Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.11; H, 6.44; N, 9.19. Compound **4e**: yield 16%, mp 180–182 °C, IR (KBr) $\nu = 2214\,cm^{-1}$ (CN), $1753\,cm^{-1}$ (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.48 (b s, 6H, $3CH_2$), 2.29 (s, 3H, CH_3), 3.05 (b s, 4H, $2NCH_2$), 3.86 (s, 3H, OCH_3), 6.91–6.96 (d, $J = 8.76$ Hz, 2H, ArH), 7.13–7.18 (d, $J = 8.78$ Hz, 2H, ArH); MS (FAB) 325 (M^++1); Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.45; H, 6.36; N, 8.65.
18. X-ray crystal data of **3c**: $C_{18}H_{18}N_2O_2$, $M = 294.4$, monoclinic, $P2_1/c$, $a = 8.875$ (1) Å, $b = 9.880$ (1) Å, $c = 18.278$ (2) Å, $\beta = 98.56$ (1)°, $V = 1584.9$ (3) Å^3, $Z = 4$, $D_c = 1.301\,g\,cm^{-1}$, μ (Mo-Kα) $= 0.09\,mm^{-1}$, $F(000) = 660.0$, brown rectangular crystal, size $0.275 \times 0.10 \times 0.075$ mm, 3786 reflections measured, 2788 unique, $R_w =$

0.11 for all data, conventional $R=0.040$ for 2024 Fo > 4sig(Fo), $S=1.026$ for all data and 200 parameters. Data of **4j**: $C_{16}H_{16}N_2O_2S$, $M=300.37$, triclinic, P-1, $a=9.472$ (1) Å, $b=9.715$ (1) Å, $c=18.483$ (1) Å, $\alpha=76.40$ (0)°, $\beta=83.75$ (1)°, $\gamma=61.81$ (1)°, $V=1457.0$ (2) Å^3, $Z=4$, $D_c=1.369\,g\,cm^{-1}$, μ (Mo-Kα) $=0.23\,mm^{-1}$, $F(000)=632.0$, brown rectangular crystal, size $0.300\times0.10\times0.075$ mm, 6102 reflections measured, 5098 unique, $R_w=0.13$ for all data, conventional $R=0.0502$ for 3263 Fo > 4sig(Fo), $S=1.021$ for all data and 381 parameters. Unit cell determination and intensity data collection ($2\theta=50°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [(Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996) was used for data collection and data processing], SHELXTL-NT [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (CCDC deposit No for **3c**: 238557 and **4j**: 238558).