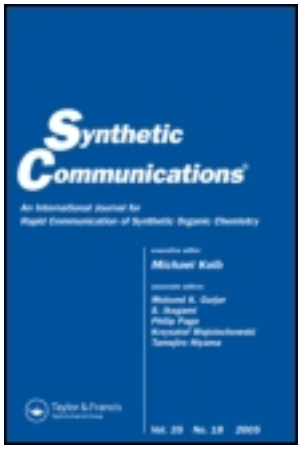

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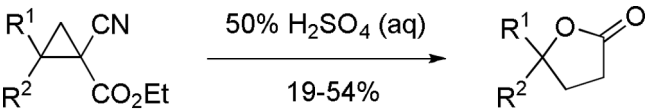
IMPROVED SYNTHESIS OF γ-LACTONES FROM CYCLOPROPYL CYANOESTERS

Nandini C. Patel, Jacob B. Schwarz, Khondaker Islam, Whitney Miller, Tuan P. Tran, and Yunjing Wei
Pfizer Global Research and Development, Groton, Connecticut, USA

GRAPHICAL ABSTRACT



2 **4**

Abstract *Cyclopropyl cyanoesters* ***2*** *were reliably converted to γ-lactones* ***4*** *on treatment with aqueous sulfuric acid. The cyanoesters could be easily prepared from ketones or aldehydes in two steps, making this process particularly attractive from an efficiency standpoint.*

Keywords Condensation; cyclopropyl cyanoester; Knoevenagel; lactone; ring expansion

INTRODUCTION

γ-Lactones constitute a class of naturally occurring substances that continue to be the target of important advances in synthetic methodology.[1] During the course of an effort directed toward the preparation and biological testing of a series of cyclopropyl β-amino acids **3**, we relied on the use of cyanoester intermediates **2**.[2] The cyanoesters were particularly valuable from an efficiency standpoint in that they could be obtained from ketones and aldehydes **1** in two steps via a facile nitroalkane cyclopropanation process.[3] Herein we report that the versatile cyclopropyl cyanoesters **2** may also be reliably converted in a single step to γ-lactones of type **4**.

To illustrate this process, 6-oxa-spiro[2.5]octane cyanoester was fashioned from ketone **5a** using standard conditions.[2] Hence, Knoevenagel condensation followed by cyclopropanation with nitromethane proceeded smoothly to afford cyanoester **2a** in 85% yield (Scheme 1). While attempting to carry out a hydrolysis reaction of **2a** with aqueous mineral acid, moderate conversion to a product that no longer contained the cyclopropane ring by ^{1}H NMR was observed. Analytical data for the compound suggested the formation of lactone **4a**. To confirm our

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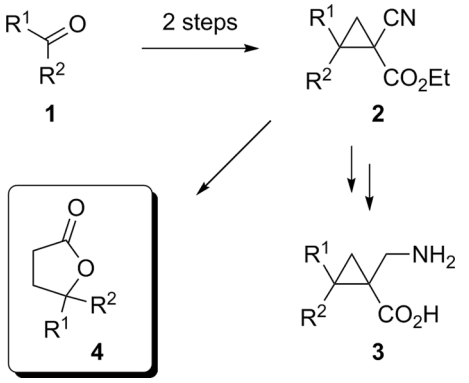
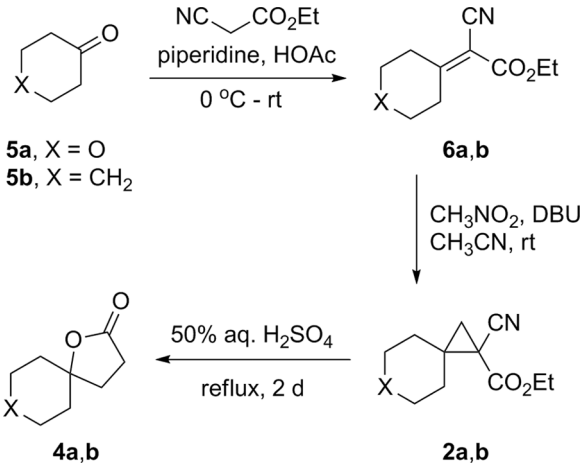


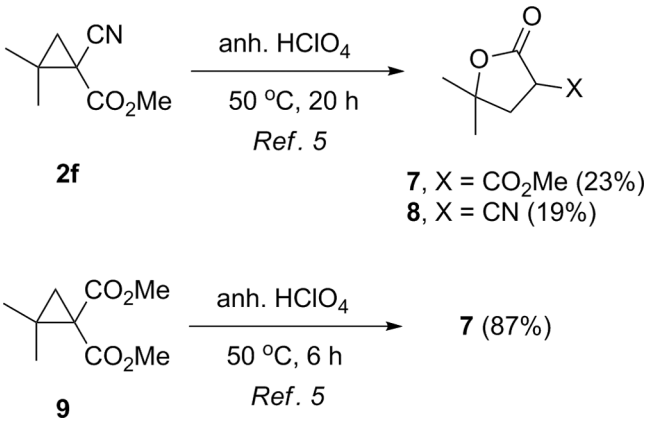
Figure 1. γ-Lactone synthesis from cyclopropyl cyanoesters.

hypothesis, cyclohexyl derivative **4b** was prepared through the same process and was consistent with literature data.[4] With the lactone products correctly identified, we then sought to gain some mechanistic insight and subsequently evaluate the scope and generality of the process.

A survey of the literature led us to a report describing protolysis of cyclopropanes containing geminal electronegative substituents (Scheme 2).[5] They found that treatment of gem-dimethyl cyanoester **2f** with anhydrous perchloric acid afforded α-carboxylactone **7** (23%), α-cyanolactone **8** (19%), as well as recovered starting material (48%). In addition, treatment of **2f** in neat trifluoracetic acid (TFA) at ambient temperature for 5 days resulted in no reaction, serving to underscore the stability of cyanoesters **2** to highly acidic media. However, when they treated diester substrate **9** under the same $HClO_4$ conditions, it was readily converted to **7**. In fact, others had shown that the diacid analog of **9** readily isomerized to the α-acid of **7** (X = CO_2H) in H_2O with $t_{1/2} \sim 3$ h.[6] Although decarboxylation of esters of type **7** have been shown to proceed in excellent yield,[7] obtaining unsubstituted lactones of type **4** would



Scheme 1. Three step synthesis of lactones **4a,b** from ketones **5a,b**.



Scheme 2. Formation of carboethoxy- and cyano-lactones **7** and **8**.

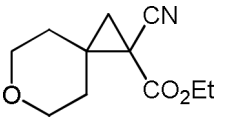
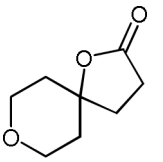
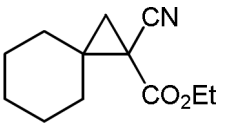
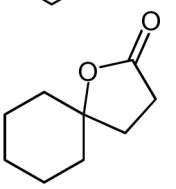
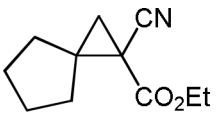
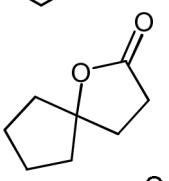
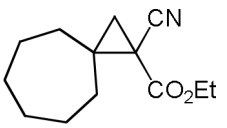
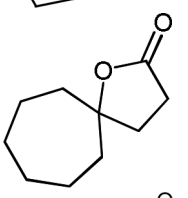
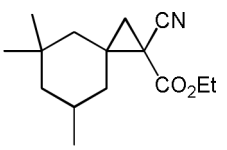
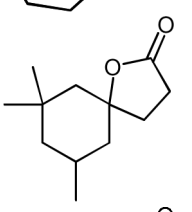
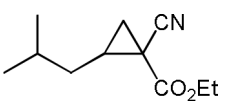
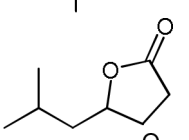
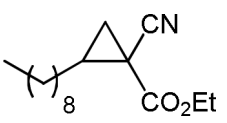
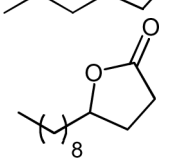
nevertheless add another step to the sequence.[8] Hence, the gain in operational efficiency, coupled with the hazards associated with the use of perchloric acid, implied that the sulfuric acid method outlined in Scheme 1 provides a distinct advantage over the existing literature processes.

Examples of spirocyclic cyclopropyl cyanoester cleavage to the γ-lactone products using sulfuric acid are shown in Table 1 (entries **a**–**e**). In all cases, the yield of isolated lactone product exceeded 35%. From liquid chromatographic/mass spectrometric (LC/MS) analysis of the reaction progress, the final decarboxylation event was rate limiting, and in the case of **1a** the α-carboxylic acid lactone was also isolated as a minor product (14% yield). The hydrolytic ring opening of less highly substituted cyclopropanes derived from aldehydes also proceeded to afford lactones, albeit in reduced yield compared to the spiro systems (entries **f**–**g**). In addition to volatility, the lower propensity to form carbocationic intermediates may have contributed to the diminished yields obtained.

Given the efficiency with which diester **9** was converted to α-methoxycarbonyl-lactone **7**, the cyanoester and diester processes were compared holistically starting from the ketone or aldehyde precursor **1**. The Knoevenagel process with malonate to produce the unsaturated diester is routinely promoted by a Lewis acid (e.g., $ZnCl_2/Ac_2O$[9] or stoichiometric $TiCl_4$[10]), and the yields obtained are generally lower than those for the cyanoacetate condensation performed with piperidinium acetate.[11] Once the diester is in hand, cyclopropanation may be performed in the same fashion as for cyanoester **6**[3] or via a bromination and hydride addition sequence.[12] Alternately, the cyclopropyl diesters may be prepared via transition-metal-catalyzed diazomalonate addition to a terminal olefin.[13] Owing to the facts that (1) the cyanoacetate Knoevenagel is catalytic and run in the absence of solvent, (2) the nitromethane cyclopropanation is robust, and (3) a separate decarboxylation step is obviated, the cyclopropyl cyanoester process is clearly more efficient (and green) than that described previously for the diesters/diacids.

In conclusion, we have developed the protolytic cleavage of cyclopropane cyanoesters into an efficient process that directly affords 5-substituted γ-lactones in moderate yield on treatment with aqueous sulfuric acid. Previously, this process

Table 1. Conversion of cyanoesters **2** to γ-lactones **4** with H_2SO_4

Entry	Cyanoester **2**	Product **4**	Yield (%)[a]
a			41
b			54
c			44
d			36
e			36
f			19
g			29

[a]Isolated yields. For procedures, see Experimental section.

was carried out with anhydrous perchloric acid, affording only a poor yield of the α-ester and α-nitrile substituted lactones. Although perchloric cleavage of related cyclopropyl diesters was shown to be a more robust process, decarboxylation of the α-carboxylate would be required to obtain lactones unsubstituted in the 3-position. In addition, cyclopropyl cyanoesters are more efficiently prepared than

their diester counterparts, making the present process more attractive and green by reducing the number of steps as well as eliminating solvent usage.

EXPERIMENTAL

Representative Procedure for Knoevenagel Condensation

Acetic acid (0.15 mL, 2.7 mmol), was added to a mixture of tetrahydro-pyran-4-one (2.68 g, 26.8 mmol) and ethyl cyanoacetate (2.9 mL, 26.8 mmol) at 0 °C followed by piperidine (0.27 mL, 2.7 mmol). The ice-water bath was removed, and 2.7 mmol portions each of acetic acid and piperidine were added. The mixture was stirred 25 min, then partitioned between EtOAc and saturated $NaHCO_3$ (aq). The phases were separated, and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated to provide 5.1 g (98%) of 1-cyano-6-oxa-spiro[2.5] octane-1-carboxylic acid ethyl ester[15] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.28 (q, $J = 7.1$ Hz, 2 H), 3.86 (t, $J = 5.5$ Hz, 2 H), 3.78 (t, $J = 5.5$ Hz, 2 H), 3.17 (t, $J = 5.5$ Hz, 2 H), 2.78 (t, $J = 5.6$ Hz, 2 H), 1.34 (q, $J = 7.1$ Hz, 3 H). ^{13}C NMR: δ 173.66, 161.80, 115.19, 103.70, 68.50, 68.24, 62.21, 36.98, 32.66, 14.28.

Representative Procedure for Cyclopropanation

Nitromethane (3.8 mL, 70.3 mmol) and DBU (2.2 mL, 14.1 mmol) were added to 1-cyano-6-oxa-spiro[2.5]octane-1-carboxylic acid ethyl ester (2.74 g, 14.1 mmol) in 60 mL acetonitrile and the whole was stirred 16 h at ambient temperature. The mixture was partitioned between EtOAc/1 N HCl (aq). The phases were separated, the aqueous phase was extracted with EtOAc, and the combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (20 → 80% EtOAc/heptane) to afford 2.57 g (87%) of 1-cyano-6-oxa-spiro[2.5]octane-1-carboxylic acid ethyl ester **2a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (q, $J = 7.1$ Hz, 2 H), 3.86 (dt, $J = 11.4$, 3.4 Hz, 1 H), 3.77 (ddd, $J = 7.4$, 3.9, 3.8 Hz, 1 H), 3.60–3.70 (m, 2 H), 1.92 (dt, $J = 17.0$, 3.2 Hz, 1 H), 1.71–1.88 (m, 4 H), 1.53 (d, $J = 5.1$ Hz, 1 H), 1.33 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR: δ 165.92, 117.86, 67.27, 67.05, 63.09, 37.08, 34.60, 29.35, 28.39, 24.38, 14.37. MS m/z 209.

Representative Procedure for Lactone Formation

A mixture of 1-cyano-6-oxa-spiro[2.5]octane-1-carboxylic acid ethyl ester **2a** (0.51 g, 2.44 mmol) in 5.0 mL 50% (v/v) aq. H_2SO_4 was stirred 2 days at 100 °C. The mixture was cooled and partitioned between EtOAc/water. The phases were separated, the aqueous phase was extracted with EtOAc, and the combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (20 → 80% EtOAc/heptane) to afford 158 mg (41%) of 1,8-dioxa-spiro[4.5]-decan-2-one **4a** as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): δ 3.71 (t, $J = 5.3$ Hz, 4 H), 2.61 (t, $J = 8.3$ Hz, 2 H), 2.09 (t, $J = 8.3$ Hz, 2 H), 1.79 (t, $J = 5.6$ Hz, 4 H). ^{13}C NMR: δ 177.64, 83.60, 64.26, 36.74, 32.52, 27.83. MS m/z 156. The by-product 2-oxo-1,8-dioxa-spiro[4.5]decane-3-carboxylic acid was also isolated (69 mg, 14%).

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