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# Glycine catalyzed diastereoselective domino-synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles in water

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The first example of glycine catalyzed directly domino- synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles in aqueous medium was described, giving products in excellent yields and up to excellent diastereoselectivities. This approach provides a highly efficient and environmentally benign access to cyano substituted 2,7-dioxabicyclo[3.2.1]octane.

## Introduction

Water is the Nature solvent for syntheses.[1] Using water as a solvent makes the synthesis more environmentally friendly and safe, which corresponds to the principles of green chemistry. Furthermore, water is also known to enhance the rates and to affect the selectivity of a wide variety of organic reactions, that increases their synthetic utility in organic chemistry.[2] Water also plays an important role as an alternative solvent replacing hazardous organic solvents for the synthesis of various heterocycles.[3]

In this paper a new method of glycine catalyzed directly synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles in aqueous medium is described. 2,7-Dioxabicyclo[3.2.1]octane moiety is an important fragment of natural compounds. There are many illustrative examples such as *Colomitides*, *Aplytangene-1*, *Macfarlandins*, *Aplyviolene*, *Polyrhaphins* etc.[4]

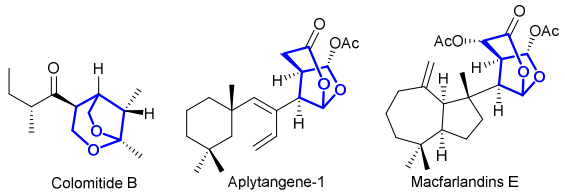


**Figure 1**. Examples of naturally occurring compounds with 2,7-dioxabicyclo[3.2.1]octane moiety

Among the compounds with 2,7-oxabicyclo[3.2.1]octane moiety substances having potent antibiotic,[5a] noticeable antifungal and antibacterial activities were found.[4a] Therapeutic compounds for the treatment of cancer,[5b] selective inhibition of α-mannosidase,[5c] potent activity in neurotrophic factor biosynthesis in glial cells,[5d] the ability to inhibit cholinesterase activity[5e] also include 2,7-oxabicyclo[3.2.1]octane moiety. Dioxabicyclo[3.2.1]octanes have also been used as key-intermediates in total synthesis of natural products (Versicolorin, Amipurimycin) and to access other classes of important heterocycles such as pyrans and furans.[6]

The most of the methods for the synthesis of 2,7-dioxabicyclo[3.2.1]octanes is based on the reactions of carbohydrates cyclization,[7a,b] on the formation of the intramolecular acetals from dihydroxyaldehydes,[7c] on the intramolecular heterocyclization of 3,4-dihydro-4-hydroxymethyl-2*H*-pyrans[7d] and on the dehydration of substituted furans containing 1,5-diol moiety.[7e] Catalytic methods are also wide-presented in the scientific literature, they include diol and triple bond cyclization in the presence of a catalyst $AuCl_3$,[5a,7f] dicobalt octacarbonyl catalyzed double [2+2+1] carbonylative cycloaddition reaction of triynes,[7g] platinum-catalyzed [4+2]cycloadditions and annulations of enynals with allylic alcohols,[7h] rhodium catalyzed cycloisomerization – hydrogenation – isomerization – acetalization aryl-substituted alkynyl allyl alcohols[7i] and heterocyclization of 2-bromomethyl-4,7-dihydro-1,3-dioxepines by $Bu_3SnH$.[7j]

## Results and discussion

We reported that 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **2** can be produced from appropriate 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** and 1,3,5-trisubstituted 2,4-diazapenta-1,4-dienes,[8a] and catch much interest as compounds with cytotoxic activity and capability to suppress the tumor cell growth.[8b]

In continuation of our research work on the construction of 2,7-dioxabicyclo[3.2.1]octane moiety, we described herein the first example of synthesis in water. This approach provides an easy access to the highly functionalized 2,7-dioxabicyclo[3.2.1]octane derivatives in environmentally friendly and mild conditions.

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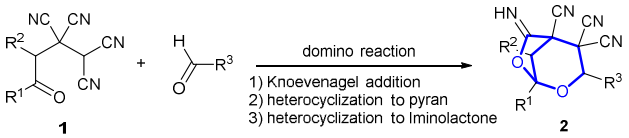
*† CCDC 1062055. For crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x*




**Scheme 1**. Domino approach to 2,7-dioxabicyclo[3.2.1]octanes

Target compounds was not yield in the absence of a catalyst, so for the initiation of the first stage (Knoevenagel addition of CH-acid **1** to the carbonyl group of aldehyde) basic catalysis was used. A series of organic and inorganic catalysts were screened for this reaction, and the obtained results are summarized in Table 1. Generally, as catalysts, inorganic and organic bases gave bad yields and led to the formation of byproducts. Reported that 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** easily react with hydroxide-anion[9a,b] or amines[9c-e] . Among all the catalysts screened, glycine emerged as the best, affording the product **2b** in a quantitative yield for 1-5 minutes.

**Table 1**. Screening of organic and inorganic catalysts of reaction 1-(2-oxocyclohexyl)ethane-1,1,2,2-tetracarbonitrile **1a** with acetaldehyde[a]

| Entry | Catalyst | Yield, % |
|---|---|---|
| 1 | None | – |
| 2 | Sodium hydroxide (10%) | – |
| 3 | Sodium hydroxide (0.5%) | 21 |
| 4 | Potassium carbonate | 17 |
| 5 | Sodium acetate | 56 |
| 6 | Ammonia | 2 |
| 7 | Diethylamine | 12 |
| 8 | Triethylamine | 34 |
| **9** | **Glycine** | **98** |

a) *Reaction conditions:* 0.001 mol of ketone **2b**, 0.001 mol of acetaldehyde, 0.0005 mol of catalyst (2 drops for entry 2, 3 and 6) stirred at 25 °C in 8 ml of water.

The syntheses of 2,7-dioxabicyclo[3.2.1]octanes were carried out in water at room temperature where the 4-oxoalkane-1,1,2,2-tetracarbonitrile **1** component was reacted in a 1 : 1.2 ratio with the aldehyde in the presence of glycine. The resulting precipitate was isolated and gave microanalytical data supporting the formulation of the desired compound (Figure 2).

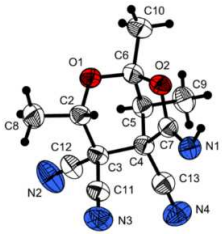
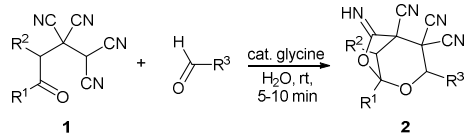



**Figure 2**. The molecular structure of **2f** with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small spheres of arbitrary radii. Distances and angles in the molecule are unexceptional and match those found in similar molecules. The crystal structure is stabilized by a N1-H1…O1*(0.5-X, 0.5+X, 1.5-Z) intermolecular (H1…O1* - 2.25Å, angle N1-H1…O1* 155.8°) interaction.

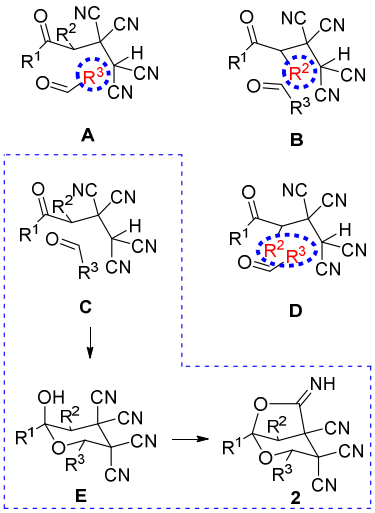
**Table 2.** Domino diastereoselective synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **2**




| Entry | Substrate | Aldehyde | Product | Yield, % |
|---|---|---|---|---|
| 1 | **1a** | | **2a** | 91 |
| 2 | **1a** | | **2b** | 98 |
| 3 | **1a** | | **2c** | 96 |
| 4 | **1a** | | **2d** | 97 |
| 5 | **1b** | | **2e** | 82 |
| 6 | **1b** | | **2f** | 94 |
| 7 | **1b** | | **2g** | 92 |
| 8 | **1b** | | **2h** | 97 |

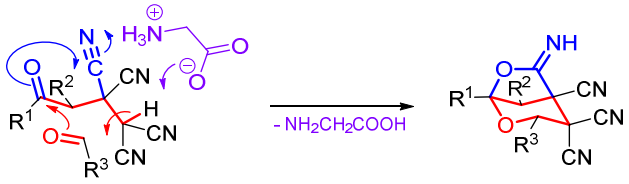
To increase wettability of 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** and to enhance the reaction rate a few drops of ethanol should be added better. After the complete conversion of 4-oxoalkane-1,1,2,2-tetracarbonitrile **1** (indicated by TLC), the water-insoluble product **2** was isolated in highly pure form just by simple filtration and washed with 1% sodium bicarbonate solution. The yields of the molecules are improvement over those previously reported for **2c,g** [8a]. The high yields obtained using this route may be due to the amphoteric nature of glycine in water, thereby promoting the condensation reaction much more effectively than using sequential acid and base reagents. Under glycine catalysis during the interaction of 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** with aldehydes only the one diastereomer

is obtained, despite the presence of four asymmetric carbon atoms including already existing in the starting compound **1**. To explain the reasons of this fact Scheme 3 is proposed. We assume that **C** is more favorable for the formation of the pyran moiety than other variants, because steric repulsions are minimal in it. Furthermore, at the approach of aldehyde to 4-oxoalkane-1,1,2,2-tetracarbonitrile **1**, as shown Scheme 3 (**C**), pyran was formed with equatorial substituents and axial hydroxyl stabilized by anomeric effect in **E** (Scheme 2).



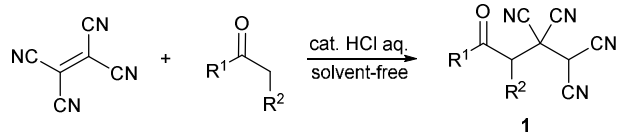
**Scheme 2.** Steric interactions of substituents during the formation of product

Glycine, except of the role of the Knoevenagel addition stage catalyst,[10] can provide the especial catalysis for the bicycle **2** formation (Scheme 3).



**Scheme 3.** Specific glycine catalysis for the formation of 2,7-dioxabicyclo[3.2.1]octane moiety

Starting compounds **1** can be easily and quantitatively obtained from corresponding ketones and tetracyanoethylene (TCNE) in solvent-free conditions (in the excess of liquid ketone) in the presence of catalytic amount of hydrochloric acid (Scheme 4).



**Scheme 4**. Synthesis of starting 4-oxoalkane-1,1,2,2-tetracarbonitriles **1**

Reaction takes place with self-heating and completes in 1-2 minutes in the case of cyclohexanone, and continuing for 1 hour at the room temperature in the case of butan-2-one.

## Conclusions

We have developed glycine catalyzed efficient synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles from appropriate aldehydes and 4-oxoalkane-1,1,2,2-tetracarbonitriles in aqueous medium. This transformation constitutes the first example of synthesis such 2,7-dioxabicyclo[3.2.1]octanes in water. This protocol is direct, operationally simple (room temperature and solvent-free purification of products) for synthesis of highly functionalized 2,7-dioxabicyclo[3.2.1]octane derivatives in excellent yields and up to excellent diastereoselectivities.

## Experimental

The progress of reactions and the purity of the products were monitored by TLC on Sorbfil plates (spots were visualized under UV light, by treatment with iodine vapor, or by heating). The IR spectra were recorded on an FSM-1202 spectrometer with Fourier transform from samples dispersed in mineral oil. The NMR spectra of **2** were measured in DMSO-$d_6$ on a Bruker DRX-500 spectrometer using tetramethylsilane as an internal reference. The mass spectra were obtained on a Bruker Ultraflex MALDI-TOF mass spectrometer. Crystals of compound **2f** suitable for X-ray analysis were grown at room temperature from chloroform solution. The data of **2f** were collected by using Cad-4 diffractometer (Cu Kα emission, λ 1.54087Å, ω-scan) Cell parameters: a= 7.534(3), b=10.682(4), c= 16.411(5)Å , β= 102.32(3)° , V=1290.3(8)Å$^3$ , space group $P2_1/n$, Z=4. Correction for absorption was not used. The structure was solved and refined with SHELX[11a] program. The non-hydrogen atoms were refined by using the anisotropic full matrix least-square procedure. The hydrogen atoms were located from a difference Fourier map and refined freely. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND[11b] software.

**Representative procedure for preparation of 1-(2-oxocyclohexyl)ethane-1,1,2,2-tetracarbonitrile 1a.**

To the 1.28 g (0.01 mol) of TCNE 1.96 g (0.02 mol) of cyclohexanone was added. Then 2 drops of concentrated hydrochloric acid to the well-stirred mixture were added and continuing stirring. After the rapid self-heating mixture became solid, important that TCNE had completely dissolved before this moment. Then 100 ml of ice-cold water poured into the reaction mixture and well stirred. Precipitated product filtered and washed with water and cooled mixture of propan-2-ol : water (1:1), then dried in the vacuum desiccator over $P_2O_5$ and kept at low temperature. Yiled 2.03 g (90%), m.p. 132–133°C (dec.) (134°C (ref. 12)).

**Representative procedure for preparation of 3-methyl-4-oxopentane-1,1,2,2-tetracarbonitrile 1b.**

To the 1.28 g (0.01 mol) of TCNE 1.42 g (0.02 mol) of butan-2-one was added. Then 2 drops of concentrated hydrochloric acid to the well-stirred mixture were added and continuing stirring at room temperature. After the completing reaction (indicated with absence of colored complex of TCNE with hydroquinone) Then 100 ml of ice-cold water poured into the reaction mixture and well stirred. Precipitated product filtered and washed with water and cooled

mixture of propan-2-ol : water (1:1), then dried in the vacuum desiccator over $P_2O_5$ and kept at low temperature. Yiled 1.72 g (86%), m.p. 134–136°C (dec.) (135-137°C (dec.) (ref. 12))

**Representative procedure for preparation of 12-imino-10,11-dioxatricyclo[5.3.2.0$^{1,6}$]dodecane-7,8,8-tricarbonitrile 2a**

To the suspension of 0.23 g (0.001 mol) 1-(2-oxocyclohexyl)ethane-1,1,2,2-tetracarbonitrile **1a** in water (8 ml), 1-2 drops of ethanol (to increase wettability of compound **1a**), 0.1 g (0.0013 mol) of 40% formaldehyde solution and 4 mg (0.0005 mol) of glycine were added. Reaction mixture stirred well at room temperature till the completing reaction (TLC). Product filtered and washed with water, 5 ml of 1% sodium bicarbonate solution and cooled mixture of propan-2-ol : water (1:1), then dried in the vacuum desiccator over $CaCl_2$. Yield 0.23 g (91%), m.p. 163-164°C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3271, 2258, 1711 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.03 (1H, m, $CH_2$), 1.26 (1H, m, $CH_2$), 1.47 (1H, m, $CH_2$), 1.72 (3H, m, $CH_2$), 2.02 (2H, m, $CH_2$), 2.82 (1H, dd, *J* 12.0 Hz, 5.8 Hz, CH), 4.16 (1H, d, *J* 12.7 Hz, $OCH_2$), 5.02 (1H, d, *J* 12.7 Hz, $OCH_2$), 9.75 (1H, s, NH). HRMS calcd. for $C_{13}H_{13}N_4O_2$ $[M+H]^+$: 257.1033, found: 257.1035.

Compounds **2b–h** were prepared in a similar manner using appropriate 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** and aldehydes.

**2b**. Yield 0.26 g (98%). M.p. 142-143 °C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3267, 2255, 1716 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.08 (1H, m, $CH_2$), 1.39 (1H, m, $CH_2$), 1.45 (3H, d, *J* 6.2 Hz, $CH_3$), 1.49 (1H, m, $CH_2$), 1.74 (3H, m, $CH_2$), 2.08 (2H, m, $CH_2$), 2.84 (1H, dd, *J* 12.0 Hz, 5.8 Hz, CH), 4.35 (1H, q, *J* 6.2 Hz, OCH), 9.78 (1H, s, NH). HRMS calcd. for $C_{14}H_{15}N_4O_2$ $[M+H]^+$: 271.1190, found: 271.1191.

**2c**. Yield 0.32 g (96%). M.p. 198-199 °C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3276, 2256, 1714 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.10 (1H, m, $CH_2$), 1.31 (1H, m, $CH_2$), 1.52 (1H, m, $CH_2$), 1.77 (2H, m, $CH_2$), 1.91 (1H, m, $CH_2$), 2.09 (1H, m, $CH_2$), 3.05 (1H, dd, *J* 11.9 Hz, 5.7 Hz, CH), 5.69 (1H, s, OCH), 7.54 (3H, m, Ph), 7.65 (2H, m, Ph), 9.87 (1H, s, NH). HRMS calcd. for $C_{19}H_{17}N_4O_2$ $[M+H]^+$: 333.1346, found: 333.1343.

**2d**. Yield 0.32 g (97%). M.p. 203-205 °C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3265, 2251, 1719 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.10 (1H, m, $CH_2$), 1.31 (1H, m, $CH_2$), 1.53 (1H, m, $CH_2$), 1.78 (2H, m, $CH_2$), 1.93 (1H, m, $CH_2$), 2.09 (1H, m, $CH_2$), 3.09 (1H, dd, *J* 11.8 Hz, 5.7 Hz, CH), 5.89 (1H, s, OCH), 7.60 (1H, dd, *J* 8.0 Hz, 4.7 Hz, Pyr), 8.07 (1H, dt, *J* 8.0 Hz, 1.9 Hz, Pyr), 8.75 (1H, dd, *J* 4.8 Hz, 1.5 Hz, Pyr), 8.87 (1H, d, *J* 2.2 Hz, Pyr), 9.93 (1H, s, NH). HRMS calcd. for $C_{18}H_{16}N_5O_2$ $[M+H]^+$: 334.1299, found: 334.1301.

**2e**. Yield 0.19 g (82%), m.p. 157-158°C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3277, 2249, 1709 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.18 (3H, d, *J* 6.8 Hz, $CH_3$), 1.54 (3H, s, $CH_3$), 2.94 (1H, q, *J* 6.8 Hz, CH), 4.11 (1H, d, *J* 12.8 Hz, $OCH_2$), 5.02 (1H, d, *J* 12.8 Hz, $OCH_2$), 9.65 (1H, s, NH). HRMS calcd. for $C_{11}H_{11}N_4O_2$ $[M+H]^+$: 231.0877, found: 231.0876.

**2f**. Yield 0.23 g (94%), m.p. 124-125°C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3275, 2261, 1719 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.19 (3H, d, *J* 6.8 Hz, $CH_3$), 1.51 (3H, d, *J* 6.0 Hz, $CH_3$), 1.54 (3H, s, $CH_3$), 2.90 (1H, q, *J* 6.8 Hz, CH), 4.53 (1H, q, *J* 6.0 Hz, OCH), 9.71 (1H, s, NH). HRMS calcd. for $C_{12}H_{13}N_4O_2$ $[M+H]^+$: 245.1033, found: 245.1035.

**2g**. Yield 0.28 g (92%), m.p. 162-163°C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3259, 2246, 1709 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.27 (3H, d, *J* 6.9 Hz, $CH_3$), 1.65 (3H, s, $CH_3$), 3.18 (1H, q, *J* 6.9 Hz, CH), 5.65 (1H, s, OCH), 7.54 (3H, m, Ph), 7.64 (2H, m, Ph), 9.79 (1H, s, NH). HRMS calcd. for $C_{17}H_{15}N_4O_2$ $[M+H]^+$: 307.1189, found: 307.1191.

**2h**. Yield 0.30 g (97%), m.p. 165-166°C (dec.). IR: $\nu_{max}$/cm$^{-1}$ 3271, 2259, 1711 cm$^{-1}$; $^1$H NMR (500 MHz; DMSO-d6, TMS) $\delta_H$ 1.28 (3H, d, *J* 6.9 Hz, $CH_3$), 1.66 (3H, s, $CH_3$), 3.31 (1H, q, $^3$*J* 6.9 Hz, CH), 5.87 (1H, s, OCH), 7.60 (1H, dd, *J* 8.0 Hz, 4.8 Hz, Pyr), 8.06 (1H, dt, *J* 8.0 Hz, 2.0 Hz, Pyr), 8.75 (1H, dd, *J* 8.0 Hz, 4.7 Hz, Pyr), 8.85 (1H, d, *J* 2.1 Hz, Pyr), 9.85 (1H, s, NH). HRMS calcd. for $C_{16}H_{14}N_5O_2$ $[M+H]^+$: 308.1142, found: 308.1140.

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**Notes and references**

§ CCDC 1062055 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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# Glycine catalyzed diastereoselective domino-synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles in water

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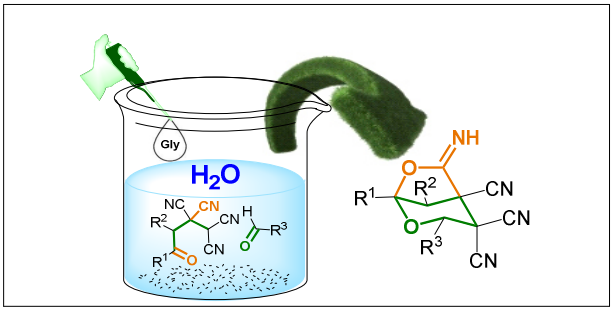


The first example of glycine catalyzed directly synthesis of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles in aqueous medium was described, giving products in excellent yields and up to excellen diastereoselectivities. This approach provides a highly efficient and environmentally benign access to cyano substituted 2,7-dioxabicyclo[3.2.1]octanes