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Relative Reactivity of *anti*- and *syn*-Oximino Carbonates and Carbamates of 2-Pyridylacetic Acid Esters

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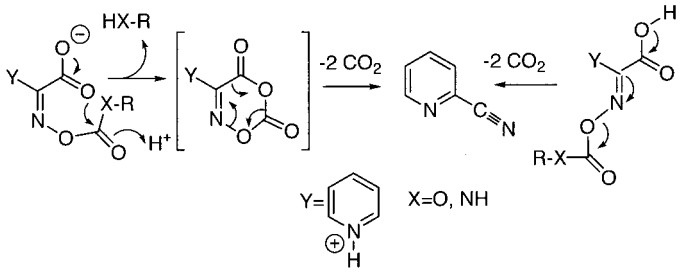
ABSTRACT

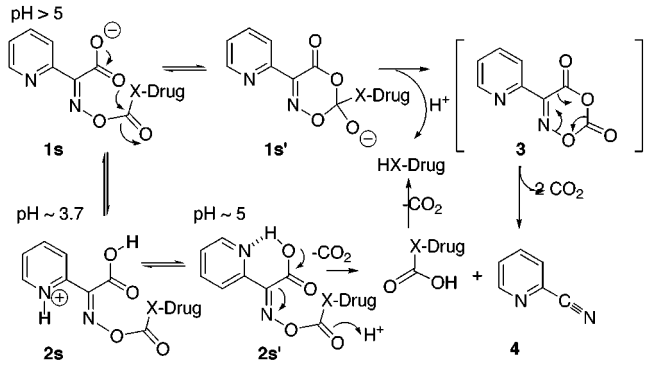


***anti*-Oximes of 2-pyridylacetic acid esters are rapidly transformed to pyridine-2-carbonitrile under a variety of conditions while *syn*-oximes bearing *tert*-butyl esters can be conveniently deprotected to the corresponding carboxylic acid with subsequent fragmentation to the nitrile.**

In conjunction with our program to utilize the folate receptor as a cell-specific mediator for the delivery of various oncolytic agents,[1] we required an intermediate capable of releasing alcohols and amines at pH values in the range of 3−7. On the basis of standard mechanistic considerations, we elected to investigate the chemistry of pyridinium carboxylates in hopes of developing a pH-triggered hydrolysis which might selectively occur at the more acidic environment found in the endosomal compartments of cancer cells.[2]

Both *syn*- and *anti*-oxime carbonates and carbamates derived from α-oxocarboxylates **1s** and **1a** were initially conceived to offer excellent opportunities for mechanism-based release of drugs bearing alcohols and amines. Scheme 1 depicts our initial hypothesis for the *syn*-oxime **1s** (as will be shown later, the *anti*-oxime−carboxylic acid **1a** could not be isolated for parallel study). It was postulated that

Scheme 1



(1) Folate Mediated Drug Delivery. 4. For papers 1, 2, and 3 see: (a) Wang, S.; Luo J.; Lantrip, D. A.; Waters, D. J.; Mathias, C. J.; Green, M. A.; Fuchs, P. L.; Low, P. S. *Bioconjugate Chem.* **1997**, *8*, 673. (b) Luo, J.; Smith, M. D.; Lantrip, D. A.; Wang, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 10004. (c) Lee, J. W.; Fuchs, P. L. *Org. Lett.* **1999**, *1*, 179.

(2) (a) Tannock, I. F.; Rotin, D. *Cancer Res.* **1989**, *49*, 4373−4384. (b) Jain, R. K. *J. Controlled Release* **1998**, *53*, 49−67.

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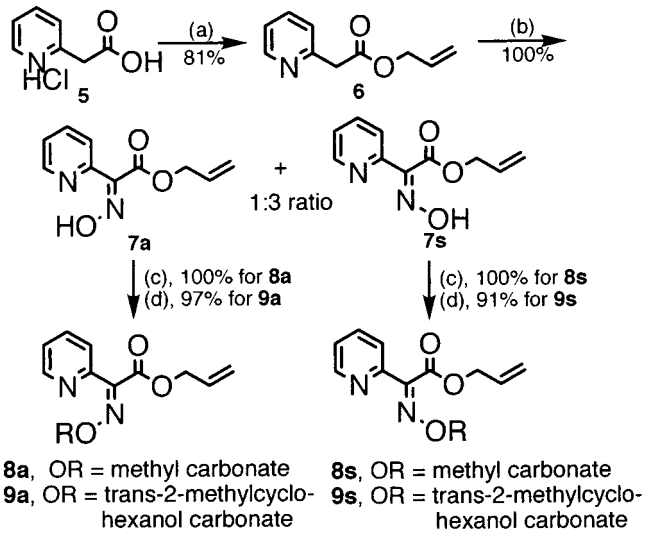
zwitterion **1s** would be present at pH values sufficient to ionize the carboxylic acid but above the anticipated pH of the protonated pyridine (~3.6−3.8[3]). Fragmentation of this species is postulated to involve intermediate **3** formed via intramolecular acylation of the carbonate (or carbamate) moiety. Completion of the process would be driven by the loss of 2 mol of carbon dioxide in concert with formation of pyridine-2-carbonitrile **4**. This fragmentation could be inhibited at pH 5 where the carboxylic acid is protonated (**2s**), or acid catalysis might enhance the intramolecular acylation sequence (**2s′**) to increase the rate.

While the 2-pyridyl moiety has been attached to aldoxime,[4] glyoxylate oxime,[5] hydrazone,[6] amides,[7] and hydroxyiminoacetate,[8] the differential reactivity of the *anti*- and *syn*-oxime isomers bearing this functionality have not been reported.

When *anti*-carbonate allyl esters **8a** and **9a** (Scheme 2**)**

Scheme 2[a]

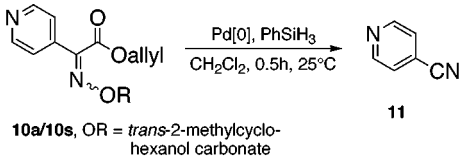


[a] Reagents and conditions: (a) Et_3N (2.0 equiv), DMAP (0.05), allyl alcohol (1.5), DCC (1.0), CH_2Cl_2, reflux, 12 h; (b) acetic acid (excess), $NaNO_2$ (1.0), water, 0−25 °C, 2 h; (c) Et_3N (2.0 equiv), methyl chloroformate (1.05), CH_2Cl_2, 25 °C, 0.5 h; (d) (i) *trans*-2-methylcyclohexanol (1.0), pyridine (1.33), triphosgene (0.33), CH_2Cl_2, reflux, 1.5 h, (ii) Et_3N (2.0), oxime starting material (1.0), 25 °C, 0.5 h.

and *syn*-carbonate **8s** were treated with 5% of $Pd[PPh_3]_4$ and 1.5 equiv of phenylsilane[9] at 25 °C for 0.5 h, pyridine-2-carbonitrile **4** was immediately produced in >97% isolated yield. No evidence of the intermediacy of the requisite carboxylic acids **1a** or **1s** was observed on TLC. Meanwhile *syn*-isomer **9s** with 5% of $Pd[PPh_3]_4$ was less reactive in dichloromethane for 1 h at 25 °C but was converted to nitrile **4** in an additional 2.5 h of stirring at the same temperature.

In the latter reaction it appeared that the pyridyl imine functionality might be operating as a bidentate ligand and sequestering the palladium[0]. In line with this hypothesis, a 1:1 mixture of *anti/syn*-4-pyridyl glyoxylates **10a/10s** resulted in rapid production of pyridine-4-carbonitrile **11**, supporting the postulate that the palladium catalyst was far more available for effecting the deallylation−fragmentation reaction (Scheme 3).

Scheme 3



Since the above allyl ester deprotection strategy did not provide access to the free carboxylic acids **1s** or **1a**, we next examined acid-catalyzed cleavage of *tert*-butyl esters **13**−**15**.[10] Each of the *syn*- and *anti*-allyl and *tert*-butyl esters shown in Schemes 2 and 4 were readily prepared from the parent pyridine acetate oximes via action of the appropriate chloroformate reagent. Single isomers were isolated using column chromatography. The structures of *syn*-oxime allyl ester **7s** and *syn*-oxime *tert*-butyl ester **12s** were determined by X-ray diffraction.[11]

As can be seen in Table 1, proton NMR chemical shift

Table 1

anti			*syn*		
no.	δH_5 (J, Hz)	δH_2 (J, Hz)	no.	δH_5 (J, Hz)	δH_2 (J, Hz)
7a	8.58δ	8.17δ	**7s**	8.66δ	7.88δ
	d, 5.9 Hz	d, 8.1 Hz		d, 4.9 Hz	d, 8.1 Hz
8a	8.75δ	7.87δ	**8s**	8.67δ	8.14δ
	d, 4.6 Hz	d, 3.6 Hz		d, 4.7 Hz	d, 7.9 Hz
9a	8.68δ	7.90δ	**9s**	8.67δ	8.15δ
	d, 3.4 Hz	m + H3		d, 4.9 Hz	d, 7.9 Hz
12a	8.57δ	7.97δ	**12s**	8.60δ	8.00δ
	d, 4.9 Hz	m + H3		d, 4.9 Hz	m + H3
13a	8.72δ	7.82δ	**13s**	8.69δ	8.12δ
	d, 4.7 Hz	m + H3		d, 4.7 Hz	d, 8.1 Hz
14a	8.72δ	7.83δ	**14s**	8.69δ	8.13δ
	d, 4.7 Hz	m + H3		d, 4.1 Hz	d, 8.0 Hz
15a	8.73δ	7.97δ	**15s**	8.70δ	8.97δ
	d, 4.2 Hz	d, 8.1 Hz		d, 4.7 Hz	d, 7.7 Hz

and coupling information on the pyridine moiety do not give a reliable indication of the *anti* or *syn* stereochemistry of

(3) *CRC Handbook of Chemistry and Physics* values for pyridine-2-carboxaldehyde and the corresponding aldoxime.

(4) Jose, B.; Sulatha, M. S.; Pillai, P. M.; Prathapan, S. *Synth. Commun.* **2000**, *30*, 1509.

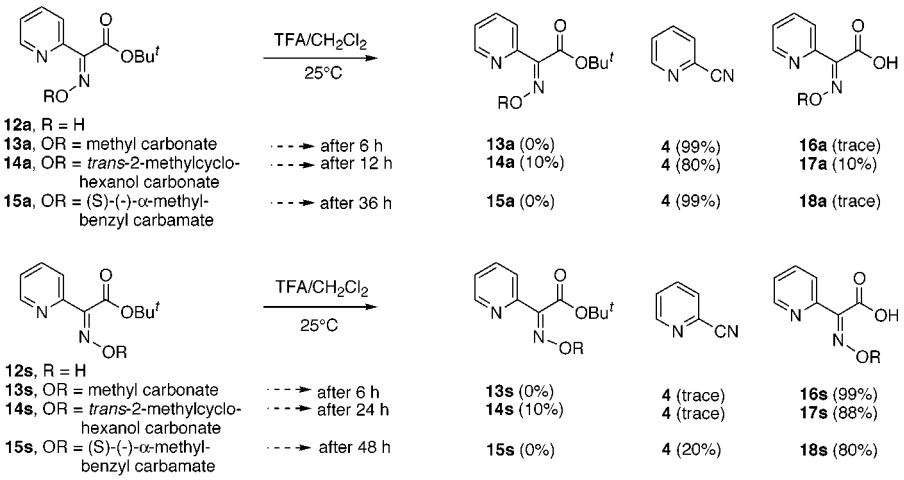
(5) Kolar, P.; Petric, A.; Tisler, M. *J. Heterocycl. Chem.* **1991**, *28*, 1715.

(6) Mathur, N. C.; Goyal, R. N.; Malik, W. U. *Indian J. Chem., Sect. A.: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **1990**. *29*, 765.

(7) Calderwood, D. J.; Davies, R. V.; Rafferty, P.; Twigger, H. L.; Whelan, H. M. *Tetrahedron Lett.* **1997**, *38*, 1241.

(8) Kolar, P.; Petric, A.; Tisler, M. *J. Heterocycl. Chem.* **1993**, *30*, 1253.

Scheme 4



the oximes and their derivatives. Once having secured the geometry of **7s** and **12s** by X-ray,[11] all other derivatives were related to these standards. As a practical note, we observed that for all the above *anti*/*syn* isomer pairs the *syn* isomer was always less polar on silica (1:2 EA/hex), consistent with the more basic nature of the *anti*-iminooxime relationship.

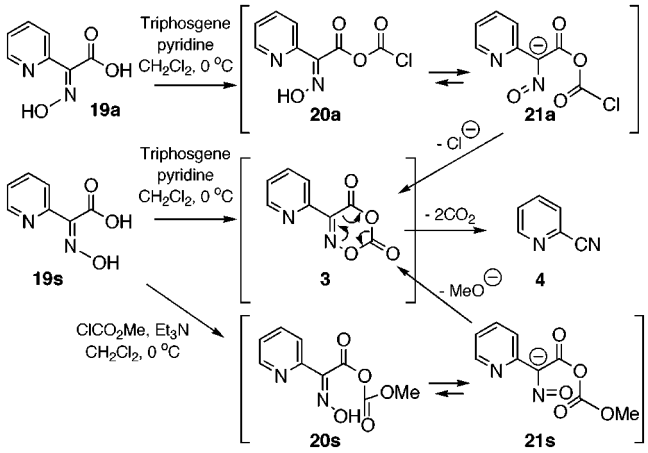
Reaction of *anti*-oximino carbonates **13a** and **14a** furnished high yields of carbonitrile **4** and only small amounts of carboxylic acids **16a** and **17a**, respectively. Oximino carbamate **15a** underwent similar decarboxylative fragmentation to nitrile **4** with only a trace of carboxylic acid **18a** being observed by TLC (Scheme 4).

In stark contrast, *syn*-carbonate **13s** furnished **16s** in essentially quantitative yield with only a trace of nitrile **4** being detected. The more sterically demanding carbonate **14s** provided acid **17s** in 88% yield after 24 h and a trace of nitrile **4**, with 10% of starting **14s** recovered. The deprotection of oximino carbamate **15s** proceeded more slowly than that of the oximino carbonates **13s** and **14s** but also delivered the *syn*-carboxylic acid **18s** in very good yield (80%).

It is interesting to note that NMR samples of **16s**, **17s**, and **18s** in DMSO-d_6 were quantitatively transformed to a 1:1 mixture of nitrile **4** and the corresponding alcohol or amine over the course of 18 h at 25 °C, demonstrating the promoting effect of a polar solvent.

In the course of our investigations, we also examined both *syn*- and *anti*-oximino acids **19s** and **19a** as potential intermediates for the synthesis of pyridyl oximino esters. As shown in Scheme 5, both acids were rapidly transformed

Scheme 5



within 5 min at 0 °C to pyridine-2-carbonitrile **4** using triphosgene. We speculate that intermediate **20a**, formed from *anti*-oxime **19a**, suffers facile deprotonation to **21a** followed by intramolecular acylation of the oximino oxygen to afford dioxazolidindione **3**, a species unknown in the chemical literature.[12] Dioxazolidindione **3** is also the likely intermediate en route from *syn*-oxime **19s** to nitrile **4**. Attempts to intercept intermediates **20a**, **20s**, or **3** by rapid quenching with excess methanol failed, and nitrile **4** was the only material detected (Scheme 5).

Reaction of oximino acid **19s** with methyl chloroformate and 2.0 equiv of triethylamine (Scheme 5) results in elimination of the alcohol moiety of the carbonate with simultaneous and quantitative production of nitrile **4**, providing credence to the mechanism proposed in Scheme 5.

We monitored both the consumption of starting material (**17s** and **18s**) and the simultaneous production of nitrile **4**

(9) (a) Thieriet, N.; Alsina, J.; Giralt, E.; Guibe, F.; Albericio, F. *Tetrahedron Lett*. **1997**, *38*, 7275−7278. (b) Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett*. **1995**, *36*, 5741−5744.

(10) The oxime esters **12s** and **12a** were prepared from **5** in parallel fashion to the synthesis of the allyl series (see Supporting Information).

(11) X-ray data from these two compounds have been forwarded to the Carbridge Crystalographic Database.

(12) Fragmentation of oxime derivatives to benzonitriles has been recently reported: Coskun, N.; Arikan, N. *Tetrahedron* **1999**, *55*, 11943.

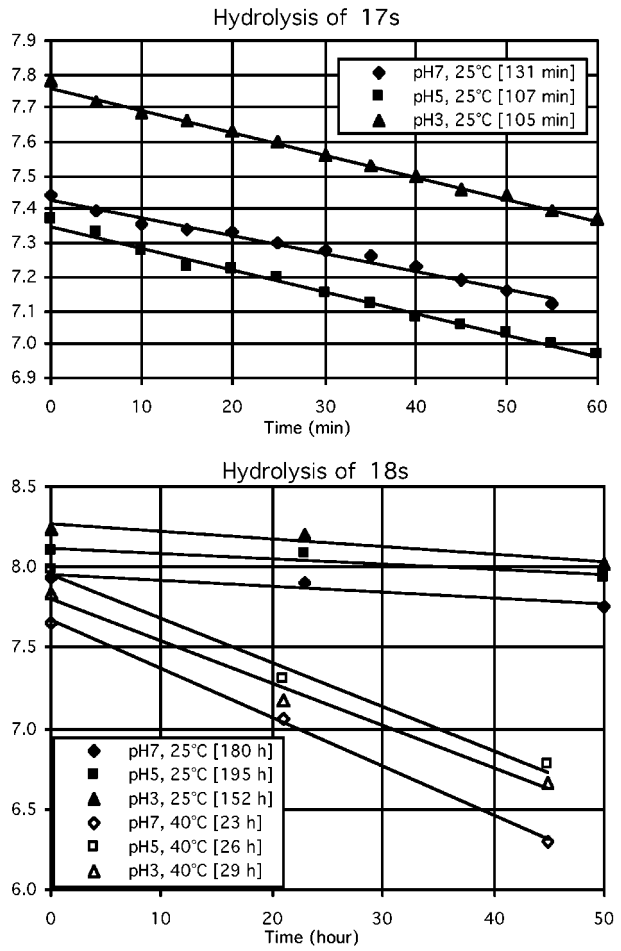


Figure 1. pH and temperature effect on hydrolysis rate. Half-lives are enclosed in brackets.

at three different pH values with HPLC.[13] When oximino carbonate **17s** was treated at 25 °C in a solution of formate buffer (pH = 3), acetate buffer (pH = 5), or phosphate buffer (pH = 7), it was observed that a *very slight* increase (~1.2) in the rate of fragmentation to **4** occurred as the reaction solution became more acidic (Figure 1). The same experiment conducted on oximino *carbamate* **18s** was substantially slower, requiring heating at 40 °C to proceed at a reasonable rate but was also *found to be essentially independent of pH* over the range examined (Figure 1). Thus, we can conclude that the mechanism is in general accord with that shown in Scheme 1, with the caveat that no significant acceleration is provided by the acid catalysis at the lower pH conditions. The ability to hydrolyze carbamate **18s** under these mild conditions attests to the likely intervention of intermediates **1s′** and **3**, as direct attack of water or hydroxide ion on the carbamoyl carbonyl would be expected to produce **19s** very slowly.

In conclusion, the reactivity of functionally differentiated 2-pyridylacetic acid esters bearing *anti*- and *syn*-oximino derivatives have been investigated under palladium-catalyzed, neutral, acidic, and basic conditions. *anti*-Oximino substrates were rapidly transformed to pyridine-2-carbonitrile **4**, while the *syn*-oximino carbonate and carbamate of the *tert*-butyl ester provided the corresponding acid as a major product using TFA to cleave the ester. Applications of variants the *syn*-pyridyl oximes as prodrugs to deliver oncolytic agents via the folate receptor are under further evaluation.

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Supporting Information Available: Experimental procedures and proton and carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) mm × 4.6 mm Econosphere C18, 50/50 acetonitrile/water, 1.0 mL/min.