

Investigación

Intramolecular Radical Addition to the 2-Pyridone Nucleus

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This paper is dedicated with affection to the memory of Dr. Raymundo Cruz Almanza

Abstract. The radical species derived from the *N*- ω -haloalkylpyridones **4b**, **6c** and the xanthates **7a**, **7b** undergo oxidative cyclization to the bicyclic 2-pyridone derivatives **8a-c** irrespective of whether they are generated under reductive ($\text{Bu}_3\text{SnH/AIBN}$) or oxidative [$\text{Fe(II)/H}_2\text{O}_2/\text{DMSO}$ or DLP] conditions.

Key words: 2-pyridone, radical cyclization, Fenton, xanthates, dilauroyl peroxide.

Resumen. Los radicales alquilo generados a partir de los correspondiente *N*- ω -haloalquilpiridonas así como de sus correspondientes xantatos, sufren ciclación oxidativa y generan las correspondientes piridonas fusionadas. Los mismos productos fueron observados tanto en condiciones reductoras ($\text{Bu}_3\text{SnH/AIBN}$) como en condiciones oxidantes [$\text{Fe(II)/H}_2\text{O}_2/\text{DMSO}$ o DLP].

Palabras clave: 2-piridona, ciclación radical, Fenton, xantatos, peróxido de dilauroilo.

Introduction

Enormous progress both in the mechanistic understanding and in the synthetic utility of free radical reactions has been achieved during the past two decades. One of the notable synthetic processes, which has been developed, is the cyclization of carbon-centered radicals to heteroaromatic systems followed by an *in situ* oxidative restoration of the aromaticity (oxidative radical cyclization) [1-4]. Several methods have been devised to effect such radical cyclizations, with *n*- Bu_3SnH -mediated reactions being the most explored [2]. The highly toxic nature of the tin reagent, and the difficulties associated with the removal of the tin containing reaction products, have led synthetic organic chemists to find alternative methods to accomplish such reactions. In this context, we have recently utilized efficient “tin-free” methods in which organic peroxides serve as both the radical initiators and the oxidants, when alkyl iodides or the corresponding xanthates were used as the radical precursors [5]. Indeed, these processes were successfully applied to oxidative radical cyclizations on benzenoid, 4-quinolone, 1-isoquinolone, pyrrole and indole systems [5]. The prominent role played by pyridones and related compounds as privileged structures in many natural products and bioactive compounds, led us to consider the extension of our

studies to the 2-pyridone nucleus. This process, if successful, would constitute a facile entry into the very important indolizidine and quinolizidine alkaloids (e. g., lupinine **1** and monomorphine **2**) [6]. In this paper we describe some of our results concerning the radical cyclization to the 2-pyridone nucleus using both reductive (*n*- Bu_3SnH) and Fenton-type [3] and dilauroyl peroxide (DLP) based oxidative conditions.

Results and Discussion

The iodides **6** and xanthates **7** required for the radical cyclizations were synthesized in two steps by *N*-alkylation [7] of the 2-pyridones **3** with the appropriate α , ω -dibromoalkane followed by either, halogen exchange with an excess of sodium iodide or, nucleophilic substitution with potassium ethyl xanthate (Scheme 1). As was observed in the 1-isoquinolone series [7], the *O*-alkylated isomers **5a** and **5c** were formed as minor byproducts during the preparation of **4a** and **4c**. This was of little consequence since these compounds were transformed into the iodides **6a** and **6c** under the equilibrating conditions of the halogen exchange reaction. Curiously, the bromide **4b** was destroyed under these conditions, but this too was of little importance since it was sufficiently reactive both to give the xanthate **7a** and to participate in radical cyclization reactions.

The radical reactions of **4b**, **6a** and **6c** were first examined using *n*- $\text{Bu}_3\text{SnH/AIBN}$ in benzene at reflux temperature. Both **4b** and **6c** gave the products of oxidative radical cyclization **8b** and **8c** in 45 % and 11 % yields, respectively, accompanied by substantial amounts of the reductive dehalogenation products **9b** and **9c** (Table 1, Scheme 2). In contrast, the iodide **6a** gave a complex mixture from which only the reductively

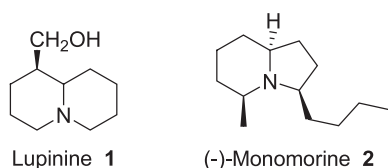
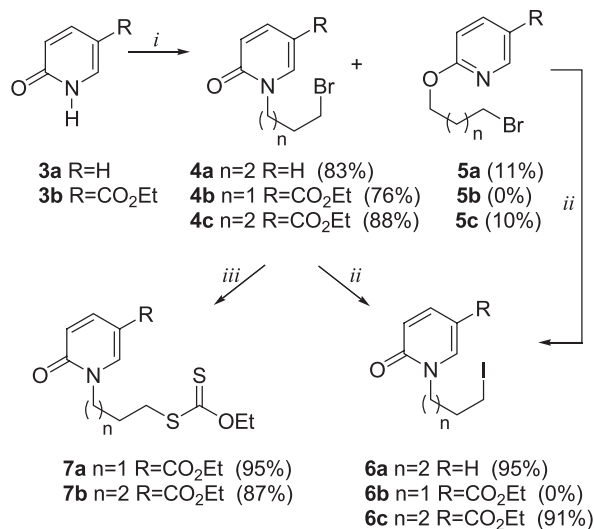


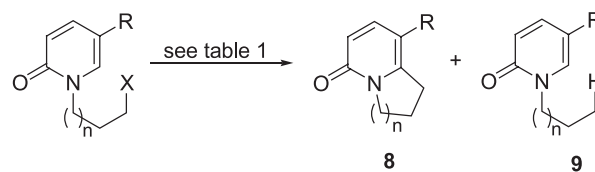
Fig. 1.



Scheme 1. Conditions: i) NaH, DMF, BrCH₂CH₂(CH₂)_nBr; ii) NaI, CH₃CN, reflux, 24 h; iii) KSC(S)OEt, CH₃CN, r. t.

dehalogenated compound **9a** could be isolated. According with these results we suggest that the presence of the strongly electron withdrawing CO₂Et ($\sigma = 0.37$) group at C-5 (e.g. **4b** and **6c**) in the pyridone ring system decrease the SOMO-LUMO energy difference at C-6 and favor radical attack at this site [2m]. The generation of **8b** and **8c** under these formally reducing conditions can no longer be considered unusual, although the nature of the oxidant can sometimes be obscure [2k]. For the examples described herein however, it is likely that AIBN is the oxidant, given that stoichiometric amounts of this radical initiator were required to achieve total consumption of the starting materials [2k].

We next turned our attention to the use of the Fenton-type conditions [Fe(II)/H₂O₂/DMSO], which have given excellent results in pyrrole, and indole systems [3]. Compounds **4b** and **6c** did give rise to the expected products **8b** and **8c**, but in exceedingly poor yields. The iodide **6a** gave a complex mixture of substances which did not contain **8a**. These disappoint-



Scheme 2.

ing results encouraged us to examine the xanthates **7a** and **7b** as radical precursors with DLP as the initiator, under conditions developed by Zard, et. al [4]. Using stoichiometric quantities of DLP in 1,2-dichloroethane at reflux temperature, both **7a** and **7b** produced the expected bicyclic 2-pyridone derivatives **8b** and **8c**. Whereas **8b** was obtained in a creditable 65 % yield, **8c** was produced with considerably less efficiency (28 %), and was admixed with a significant quantity of the dithiocarbonate **11** (Scheme 3). The formation of **11** implies that the rate of attack of the radical **10** on the xanthate **7b** (Scheme 3, path β) is competitive with its cyclization to **8b** (Scheme 3, path α).

Although the radical cyclizations described herein were generally of modest efficiency, nevertheless they are the first reported examples of the intramolecular addition of alkyl radicals to the 2-pyridone system. It is noteworthy that such cyclizations have previously been reported to fail under typical *n*-Bu₃SnH/AIBN mediated conditions [8].

Conclusions

The first examples of the intramolecular oxidative addition of alkyl radicals to the 2-pyridone system are described.

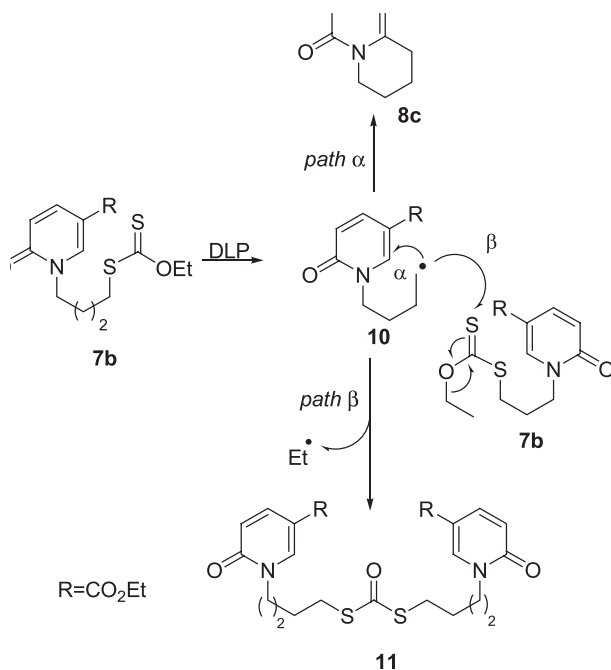
Experimental Section

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were

Table 1. Radical cyclization.

Entry	Substrate	X	n	R	Cond.	Product,	yield (%)
1	6a	I	2	H	A	8a (0)	9a (35)
2	4b	Br	1	CO ₂ Et	A	8b (45)	9b (27)
3	6c	I	2	CO ₂ Et	A	8c (11)	9c (29)
4	6a	I	2	H	B	8a (0)	-
5	4b	Br	1	CO ₂ Et	B	8b (13)	-
6	6c	I	2	CO ₂ Et	B	8c (9)	-
7	7a	SC(S)OEt	1	CO ₂ Et	C	8b (65)	-
8	7b	SC(S)OEt	2	CO ₂ Et	C	8c (28)	11 (21)

Conditions: A) *n*-Bu₃SnH (1.2 eq.), AIBN (1.2 eq.), Benzene, reflux; B) FeSO₄•7H₂O, H₂O₂, DMSO,); C) Dilauroyl peroxide (1.1 eq.), dichloroethane, reflux.



Scheme 3.

distilled before using them. Silica gel (230-400 mesh) was purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher-Johns melting point apparatus and they are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

Synthesis of the Bromo Compounds 4a-4c. To a suspension of NaH (60% in mineral oil, 1.2 equiv), in anhydrous DMF (1 mL/equiv substrate) and DME (4 mL/equiv substrate) was added a solution of the *N*-unsubstituted pyridone (1 equiv) in DME at 0 °C. After 10 min, the reaction mixture was treated with LiBr (2 equiv) and stirred for 15 min, then α,ω -dibromoalkane in DME was added dropwise. The reaction mixture was stirred at room temperature for 1-6 h and then quenched with ice water. The mixture was extracted with ethyl acetate, the combined organic layer was washed successively with water and saturated sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate mixtures to elute the product.

1-(4-Bromobutyl)-1*H*-pyridin-2-one (4a). Eluted with hexane-ethyl acetate (7:3) in 83% yield as an oil; IR (CHCl_3) ν_{max} :

2945, 2866, 1657, 1588, 1538 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.88-1.95 (4H, m), 3.41-3.47 (2H, m), 3.98 (2H, t, J = 7.0 Hz), 6.20 (1H, t, J = 6.7 Hz), 6.57 (1H, d, J = 8.8 Hz), 7.28-7.38 (2H, m); ^{13}C NMR (CDCl_3 , 75 MHz) δ 27.8, 29.4, 32.9, 48.6, 106.2, 120.8, 137.3, 139.4, 162.5; MS (EI) m/z (rel. intensity) 229 (M^+ , 25), 231 (24), 150 (100).

Ethyl 1-(3-Bromopropyl)-1*H*-pyridin-2-one-5-carboxylate (4b). Eluted with hexane-ethyl acetate (1:1) in 76% yield as a white solid mp 75-76 °C; IR (KBr) ν_{max} : 2980, 2870, 1714, 1665, 1609, 1543 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.37 (3H, t, J = 7.2 Hz), 2.36 (2H, quintet, J = 6.8 Hz), 3.43 (2H, t, J = 6.8 Hz), 4.15 (2H, t, J = 6.8 Hz), 4.33 (2H, q, J = 7.2 Hz), 6.54 (1H, d, J = 10.0 Hz), 7.87 (1H, dd, J = 2.2, 10.0 Hz), 8.23 (1H, d, J = 2.2 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.1, 29.6, 30.9, 49.1, 60.9, 110.0, 119.6, 138.6, 142.8, 162.2, 163.8; MS (EI) m/z (rel. intensity) 287 (M^+ , 10), 289 (9), 208 (100).

Ethyl 1-(4-Bromobutyl)-1*H*-pyridin-2-one-5-carboxylate (4c). Eluted with hexane-ethyl acetate (8:2) in 76% yield as a white solid mp 58-59 °C; IR (KBr) ν_{max} : 2959, 2875, 1712, 1656, 1608, 1540 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.37 (3H, t, J = 7.2 Hz), 1.91-1.96 (4H, m), 3.45 (2H, t, J = 6.8 Hz), 4.03 (2H, t, J = 6.8 Hz), 4.33 (2H, q, J = 7.2 Hz), 6.58 (1H, d, J = 10 Hz), 7.87 (1H, dd, J = 10.0, 2.2 Hz), 8.18 (1H, d, J = 2.2 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.3, 27.9, 29.5, 32.5, 49.4, 61.1, 110.3, 119.8, 138.5, 142.5, 162.4, 164.2; MS (EI) m/z (rel. intensity) 301 (M^+ , 15), 303 (14), 222 (100).

Synthesis of the Iodides 6a, 6c. A solution of the bromide (1 equiv) in acetonitrile (30 mL/g bromide) containing sodium iodide (3-4 equiv) was heated at reflux temperature for 6-24 h. The solution was poured into water and extracted with dichloromethane. The extract was washed with saturated aqueous sodium sulfite solution and water, and then it was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate mixtures to elute the product.

1-(4-Iodobutyl)-1*H*-pyridin-2-one (6a). Eluted with hexane-ethyl acetate (7:3) in 95% yield as an oil; IR (CHCl_3) ν_{max} : 2943, 2862, 1658, 1586, 1537 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.84-1.91 (4H, m), 3.18-3.25 (2H, m), 3.96 (2H, t, J = 7.0 Hz), 6.18 (1H, t, J = 6.7 Hz), 6.56 (1H, d, J = 8.8 Hz), 7.23-7.36 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 5.8, 30.1, 30.4, 48.4, 106.1, 120.8, 137.1, 139.4, 162.5; MS (EI) m/z (rel. intensity) 277 (M^+ , 25), 150 (100).

Ethyl 1-(4-Iodobutyl)-1*H*-pyridin-2-one-5-carboxylate (6c). Eluted with hexane-ethyl acetate (7:3) in 80% yield as a pale yellow solid mp 65-67 °C; IR (KBr) ν_{max} : 2959, 1712, 1656, 1607, 1539 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.37 (3H, t, J = 7.2 Hz), 1.86-1.91 (4H, m), 3.22 (2H, t, J = 6.8 Hz), 4.00 (2H, t, J = 6.8 Hz), 4.34 (2H, q, J = 7.2 Hz), 6.53

(1H, d, $J = 10$ Hz), 7.85 (1H, dd, $J = 10.0, 2.2$ Hz), 8.14 (1H, d, $J = 2.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 5.1, 14.3, 30.1, 30.2, 49.2, 61.0, 110.2, 119.8, 138.5, 142.4, 162.4, 164.2; MS (EI) m/z (rel. intensity) 349 (M^+ , 15), 222 (100); HRMS (FAB+): calcd for $\text{C}_{12}\text{H}_{17}\text{INO}_3$: 350.0253, found: 350.0247.

Synthesis of the Xanthates 7a and 7b. A solution of the bromide (1 equiv) in acetonitrile (30 mL/g bromide) containing *O*-ethylxanthic acid, potassium salt (1.2 equiv) was stirred at room temperature for 2 h. The solution was poured into water and extract with dichloromethane. The extract was washed with water, and then it was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate mixtures to elute the product.

Dithiocarbonic acid *O*-ethyl ester *S*-[3-(3-carboethoxy-2-oxo-1H-pyridin-1-yl)-propyl]ester (7a). Eluted with hexane-ethyl acetate (8:2) in 95% yield as a white solid mp 49–50 °C; IR (KBr) ν_{max} : 2937, 2871, 1715, 1664, 1612, 1543 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.37 (3H, t, $J = 7.2$ Hz), 1.42 (3H, t, $J = 7.2$ Hz), 2.2 (2H, quintet, $J = 7.0$ Hz), 3.17 (2H, t, $J = 7.0$ Hz), 4.07 (2H, t, $J = 7.0$ Hz), 4.34 (2H, q, $J = 7.2$ Hz), 4.64 (2H, q, $J = 7.2$ Hz), 6.54 (1H, d, $J = 10$ Hz), 7.85 (1H, dd, $J = 10.0, 2.2$ Hz), 8.14 (1H, d, $J = 2.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.7, 14.3, 28.0, 32.4, 49.3, 61.0, 70.1, 110.1, 119.8, 138.6, 142.6, 162.3, 164.0, 213.9; MS (EI) m/z (rel. intensity) 329 (M^+ , 55), 208 (100); HRMS (FAB+): calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{NS}_2$: 330.0834, found: 330.0834.

Dithiocarbonic acid *O*-ethyl ester *S*-[4-(3-carboethoxy-2-oxo-1H-pyridin-1-yl)-butyl]ester (7b). Eluted with hexane-ethyl acetate (7:3) in 87% yield as a white solid mp 65–66 °C; IR (KBr) ν_{max} : 2940, 1714, 1666, 1610, 1543, 1445, 1292 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.36 (3H, t, $J = 7.2$ Hz), 1.41 (3H, t, $J = 7.2$ Hz), 1.72–1.95 (m, 4H), 3.17 (2H, t, $J = 6.9$ Hz), 4.02 (2H, t, $J = 6.9$ Hz), 4.31 (2H, q, $J = 7.2$ Hz), 4.64 (2H, q, $J = 7.2$ Hz), 6.54 (1H, d, $J = 10$ Hz), 7.84 (1H, dd, $J = 10.0, 2.2$ Hz), 8.15 (1H, d, $J = 2.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.7, 14.2, 25.5, 28.3, 35.0, 49.8, 61.0, 69.9, 110.1, 119.6, 138.5, 142.5, 162.3, 164.1, 214.5; MS (EI) m/z (rel. intensity) 343 (M^+ , 5), 222 (100); HRMS (FAB+): calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{NS}_2$: 344.0990, found: 344.0995.

General Procedure for Radical Cyclization Using Dilauroyl Peroxide. To a degassed solution of the corresponding xanthate derivative (1.0 equiv) in refluxing dichloroethane (7 mL/mmol) was added dilauroyl peroxide (1.2 equiv) portionwise (0.3 equiv/1.5 h). The reaction was carried out under an atmosphere of N_2 during 7.5 h. Then, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate mixtures to elute the product.

Ethyl 4-oxo-6,7,8,9-tetrahydro-4H-quinolizine-1-carboxylate (8b). Eluted with hexane-ethyl acetate (7:3) in 65% yield

as a white solid mp 102–104 °C; IR (KBr) ν_{max} : 1686, 1643 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.34 (3H, t, $J = 7.1$ Hz), 2.22 (2H, quintet, $J = 7.6$ Hz), 3.54 (2H, t, $J = 7.9$ Hz), 4.17 (2H, t, $J = 7.4$ Hz), 4.29 (2H, q, $J = 7.1$ Hz), 6.48 (1H, d, $J = 9.5$ Hz), 7.92 (1H, d, $J = 9.5$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 20.5, 33.8, 49.4, 60.8, 106.6, 116.4, 140.6, 157.3, 162.2, 164.6; MS (EI) m/z (rel. intensity) 207 (M^+ , 100).

Ethyl 4-oxo-6,7,8,9-tetrahydro-4H-quinolizine-1-carboxylate (8c). Eluted with hexane-ethyl acetate (6:4) in 28% yield as a white solid mp 54–56 °C; IR (KBr) ν_{max} : 1701, 1650 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.36 (3H, t, $J = 7.2$ Hz), 1.41 (3H, t, $J = 7.2$ Hz), 1.77–2.01 (m, 4H), 3.38 (2H, t, $J = 6.4$ Hz), 4.06 (2H, t, $J = 6.2$ Hz), 4.29 (2H, q, $J = 7.2$ Hz), 6.46 (1H, d, $J = 9.5$ Hz), 7.92 (1H, d, $J = 9.5$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 14.2, 18.1, 21.3, 26.7, 42.3, 60.5, 107.7, 115.2, 139.6, 155.5, 162.8, 165.2; MS (EI) m/z (rel. intensity) 221 (M^+ , 100); HRMS (FAB+): calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3$: 222.1130, found: 222.1123.

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