Aroylnitrile Oxide Cyclizations. 2. Synthesis of (3-Aroylisoxazol-5-yl)alkanoic Acids

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Intermolecular cyclization of 1,3-dipolar aroylnitrile oxides to terminal alkynols followed by phase transfer catalyzed oxidation provided a short, convenient route to several novel (3-aroylisoxazol-5-yl)alkanoic acids.

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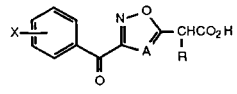
In the context of our antiinflammatory/analgesic research program, we have recently reported on the synthesis of the (3-aroyl-1,2,4-oxadiazol-5-yl)acetic acids **1** [1]. Due to the potential lability of these compounds toward decarboxylation, we sought to prepare the related (3-aroylisoxazol-5-yl)acetic acids (**2**). Along with being expectedly more stable, these isoxazole derivatives would be readily derived from an extension of our aroylnitrile oxide methodology.

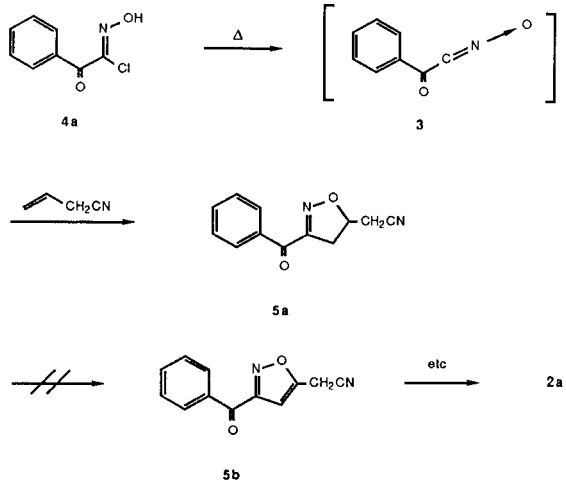


1 A = N

2 A = CH

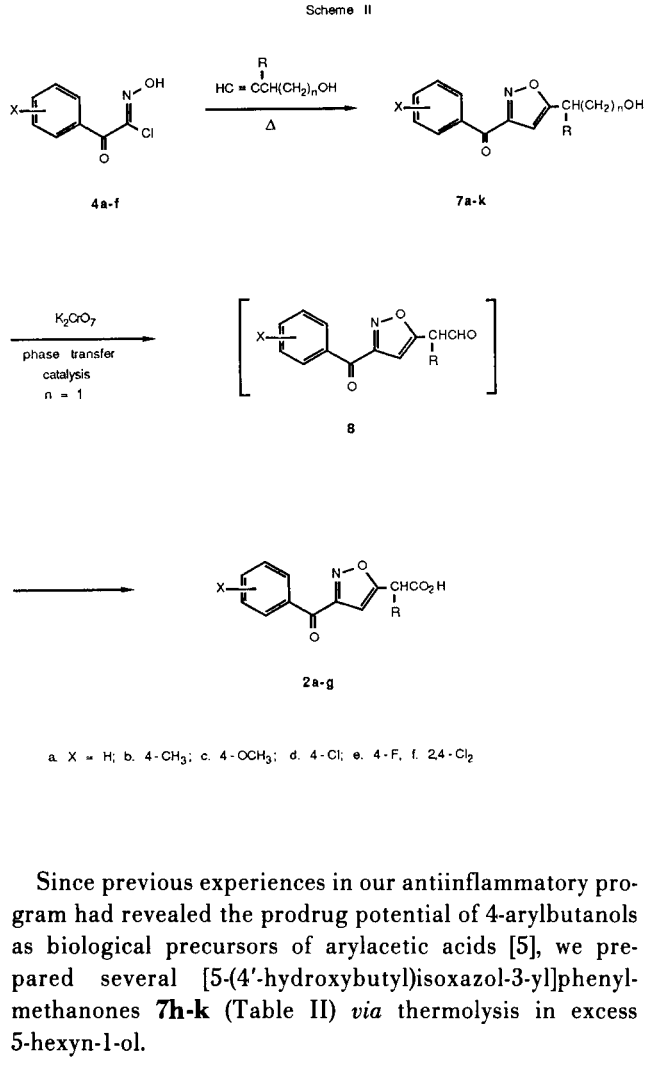
Initially, we felt that the synthetic approach outlined in Scheme I would be particularly suitable. Indeed, thermal *in situ* generation of benzoylnitrile oxide **3** [2] by refluxing a mixture of phenylglyoxylohydroxamyl chloride (**4a**) and excess allyl cyanide for 3 hours provided cycloadduct **5a** regiospecifically in 66% yield. However, attempted dehydrogenation of **5a** to the corresponding isoxazoleacetonitrile **5b** with activated γ-manganese dioxide [3] failed under a variety of conditions.

Scheme I



Subsequently, a more viable, direct route was established as outlined in Scheme II. Refluxing nitrile oxide precursors **4a-f** with excess 3-butyn-1-ol generated a variety of [5-(2′-hydroxyalkyl)isoxazol-3-yl]phenylmethanones **7a-f** in good yields (see Table I). For the preparation of an α-methylacetic acid analog, precursor **4d** was refluxed with excess 2-methyl-3-butyn-1-ol [4] to yield propanol **7g** in 59% yield.

Scheme II

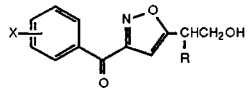


a. X = H; b. 4-CH_3; c. 4-OCH_3; d. 4-Cl; e. 4-F, f. 2,4-Cl_2

Since previous experiences in our antiinflammatory program had revealed the prodrug potential of 4-arylbutanols as biological precursors of arylacetic acids [5], we prepared several [5-(4′-hydroxybutyl)isoxazol-3-yl]phenylmethanones **7h-k** (Table II) *via* thermolysis in excess 5-hexyn-1-ol.

Table I

[5-(2'-Hydroxyalkyl)isoxazol-3-yl]phenylmethanones

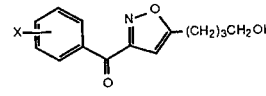


					Analysis					
					Calcd.			Found		
	X	R	Yield, %	Formula	C	H	N	C	H	N
7a	H	H	67	$C_{12}H_{11}NO_3$	66.35	5.11	6.45	66.49	5.22	6.29
7b	4-CH_3	H	67	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.30	5.69	5.69
7c	4-OCH_3	H	71	$C_{13}H_{13}NO_4$	63.14	5.31	5.66	62.74	5.45	5.56
7d	4-Cl	H	85 [a]	$C_{12}H_{10}ClNO_3$	57.27	4.01	5.57	57.66	4.18	5.39
7e	4-F	H	37 [b]	$C_{12}H_{10}FNO_3$	61.27	4.29	5.95	61.30	4.47	5.84
7f	2,4-Cl_2	H	58 [c]	$C_{12}H_9Cl_2NO_3$	50.37	3.18	4.89	50.52	3.20	4.71
7g	4-Cl	CH_3	59	$C_{13}H_{12}ClNO_3$	58.76	4.55	5.27	59.13	4.73	5.15

[a] Mp 59-62°. [b] Mp 42-45°. [c] Mp 78-80°.

Table II

[5-(4'-Hydroxybutyl)isoxazol-3-yl]phenylmethanones

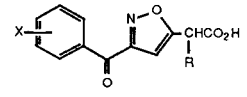


				Analysis					
				Calcd.			Found		
	X	Yield, %	Formula	C	H	N	C	H	N
7h	H	62	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.63	6.19	5.52
7i	4-CH_3	68	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	69.38	6.61	5.31
7j	4-Cl	78 [d]	$C_{14}H_{14}ClNO_3$	60.11	5.04	5.01	60.14	5.12	4.84
7k	2,4-Cl_2	78	$C_{14}H_{13}Cl_2NO_3$	53.52	4.18	4.46	53.63	4.38	4.20

[d] Mp 48-51°.

Table III

(3-Aroylisoxazol-5-yl)alkanoic Acids



						Analysis					
						Calcd.			Found		
	X	R	Yield, %	Mp°C	Formula	C	H	N	C	H	N
2a	H	H	43	108-110	$C_{12}H_9NO_4$	62.34	3.92	6.06	62.55	3.95	6.20
2b	4-CH_3	H	43	105-107	$C_{13}H_{11}NO_4$	63.67	4.52	5.71	63.57	4.49	5.69
2c	4-OCH_3	H	9	119-121	$C_{13}H_{11}NO_5$	59.76	4.25	5.36	59.49	4.21	5.32
2d	4-Cl	H	32	126-128	$C_{12}H_8ClNO_4$	54.25	3.04	5.27	54.08	3.05	5.23
2e	4-F	H	41	113-115	$C_{12}H_8FNO_4$	57.83	3.24	5.62	57.60	3.34	5.57
2f	2,4-Cl_2	H	26	108-109	$C_{12}H_7Cl_2NO_4$	48.03	2.36	4.67	47.83	2.44	4.59
2g	4-Cl	CH_3	13	122.5-124.5	$C_{13}H_{10}ClNO_4$	55.83	3.60	5.01	55.46	3.51	4.95

Methodology for chemoselective oxidation of 2-arylethanols to arylacetic acids had not been reported at the time of this investigation. Thus, we set out to perform stepwise oxidation of **7a-g** to the corresponding aldehydes **8** *via* a recently reported phase transfer catalyzed potassium dichromate procedure [6]. In our hands, none of the expected aldehyde **8a** was obtained under a variety of stoichiometric conditions [7]. Serendipitously, treatment of alcohols **7a-g** in dichloromethane with one molar equivalent of potassium dichromate in 9*M* sulfuric acid and a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate at room temperature provided the target alkanoic acids **2a-g** directly (see Table III).

Compounds **7h-k** and **2a-g** were less active than reference compounds in antiinflammatory/analgetic screening.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam SP3-200 spectrophotometer. Nuclear magnetic resonance spectra were taken on a JEOL C-60HL and chemical shifts are given relative to internal tetramethylsilane. Mass spectra were obtained from a Finnigan Model 4000 spectrometer equipped with an INCOS data system. Elemental analysis were performed by Micro-Tech Laboratories, Skokie, Illinois. Thin layer chromatograms were run on silica gel PF-254 plates (E. Merck, AG) and high performance liquid chromatography was carried out with a Waters Prep LC/System 500 using standard silica gel prepacked cartridges.

Arylglyoxylohydroxamyl Chlorides **4a-f**.

Compounds **4a-e** were prepared as previously described [1].

2,4-Dichlorophenylglyoxylohydroxamyl Chloride (**4f**).

This compound was prepared as above. Workup included concentration, trituration with hexane and recrystallization from cyclohexane to give 49% yield of white crystals, mp 100-101°; ir (chloroform): 3530, 1700 cm^{-1}; nmr (deuteriochloroform): δ 7.20-7.60 (m, 2, aromatic H), 8.74 (s, 1, OH); ms: $(MH)^+$ m/e 252.

Anal. Calcd. for $C_8H_4Cl_2NO_2$: C, 38.06; H, 1.60; N, 5.55. Found: C, 38.29; H, 1.61; N, 5.62.

(3-Benzoyl-4,5-dihydro-1,2-oxazol-5-yl)acetonitrile (**5**).

A mixture of phenylglyoxylohydroxamyl chloride (**4a**) (12.0 g, 66 mmoles) and allyl cyanide (26.5 ml, 330 mmoles) was refluxed under nitrogen for 3.5 hours. Concentration and high performance liquid chromatography using ethyl acetate:dichloromethane:hexane (5:45:50) gave 9.2 g (66%) of a light yellow oil, ir (chloroform): 2225, 1655 cm^{-1}; nmr (deuteriochloroform): δ 2.80 (d, 2, J = 10 Hz, CH_2CN), 3.0-4.0 (m, 2, CH_2), 4.80-5.35 (m, 1, CH), 7.20-7.90 (m, 3, aromatic H), 8.10-8.45 (m, 2, aromatic H); ms: M^+ m/e 214.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.20; H, 4.83; N, 12.90.

[5-(2′-Hydroxyethyl)isoxazol-3-yl]phenylmethanone (**7a**).

A solution of **4a** (12.0 g, 66 mmoles) in 3-butyn-1-ol (30 ml, 394 mmoles) was refluxed under nitrogen for 3 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 9.6 g (67%) of an oil; ir (chloroform): 3600, 1665 cm^{-1}; nmr (deuteriochloroform): δ 3.09 (t, 3, J = 10 Hz, CH_2), 3.10 (s, 1, OH), 4.00 (t, 2, J = 10 Hz, CH_2O), 6.76 (s, 1, isoxazole H), 7.40-8.00 (m, 3, aromatic H), 8.25-8.70 (m, 2, aromatic H); ms: M^+ m/e 217.

Compounds **7b-e** were prepared similarly and details are given in Table I.

[5-(2′-(1′-Hydroxypropyl))isoxazol-3-yl]-4-chlorophenylmethanone (**7g**).

A solution of **4d** (8.7 g, 40 mmoles) in 2-methyl-3-butyn-1-ol (16.7 g, 200 mmoles) [4] was refluxed under nitrogen for 3 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 6.3 g (59%) of an oil that solidified on standing, mp 49-51°; ir (chloroform): 3600, 1665 cm^{-1}; nmr (deuteriochloroform): δ 1.41 (d, 3, J = 11 Hz, CH_3), 2.25 (bs, 1 , OH), 3.31 (sextet, 1, J = 9, 11 Hz, CH), 3.90 (d, 2, J = 9 Hz, CH_2O), 6.76 (s, 1, isoxazole H), 7.60 (d, 2, aromatic H), 8.45 (d, 2, aromatic H): ms: M^+ m/e 265.

[5-(4′-(1-Hydroxybutyl))isoxazol-3-yl]phenylmethanone (**7h**).

A solution of **4a** (12.0 g, 66 mmoles) in 5-hexyn-1-ol (30 g, 306 mmoles) was refluxed under nitrogen for 4 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 10.0 g (62%) of an oil, ir (chloroform): 3600, 1660 cm^{-1}; nmr (deuteriochloroform): δ 1.40-2.10 (m, 4, CH_2), 2.23 (s, 1, OH), 2.89 (t, 2, J = 11 Hz, Het-CH_2), 3.68 (t, 2, J = 11 Hz, CH_2O), 6.60 (s, 1, isoxazole H), 7.30-7.90 (m, 3, aromatic H), 8.10-8.55 (m, 2, aromatic H); ms: M^+ m/e 245.

Compounds **7i-k** were prepared similarly and details are given in Table II.

(3-Benzoylisoxazol-5-yl)acetic Acid (**2a**).

Pulverized potassium dichromate (11.9 g, 41 mmoles) was added to a mixture of **7a** (8.8 g, 41 mmoles), one liter of dichloromethane, 150 ml of 9*M* sulfuric acid and a few crystals of tetra-*n*-butylammonium hydrogen sulfate. The resulting mixture was stirred at room temperature for 1.5 hours. After settling, the mixture was decanted and the aqueous phase was extracted with dichloromethane. The organic extract was washed with water and brine, and dried (magnesium sulfate). Concentration, followed by trituration with cyclohexane and recrystallization from toluene gave 4.0 g (43%) of a tan solid, mp 108-110°; ir (potassium bromide): 1720, 1660 cm^{-1}; nmr (DMSO-d_6): δ 4.14 (s, 2, CH_2), 6.98 (s, 1, isoxazole H), 7.40-7.95 (m, 3, aromatic H), 8.05-8.45 (m, 2, aromatic H), 12.8 (bs, 1, CO_2H); ms: $(MH)^+$ m/e 232.

Compounds **2b-e** were prepared similarly and details are given in Table III.

2-[3-(4′-Chlorobenzoyl)isoxazol-5-yl]propionic Acid (**2g**).

This compound was prepared as described above in 13% yield after two recrystallizations from toluene as a white solid, mp 122.5-124.5°; ir (potassium bromide): 1705, 1665 cm^{-1}; nmr (DMSO-d_6): δ 1.54 (d, 3, J = 12 Hz, CH_3), 4.09 (q, 1, J = 12 Hz, CH), 6.79 (s, 1, isoxazole H), 7.55 (d, 2, aromatic H), 8.15 (d, 2, aromatic H), 10.10 (bs, 1, CO_2H); ms: $(MH)^+$ m/e 280.

Acknowledgement.

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[7] Molar ratios of potassium dichromate to alcohol **7a** from 0.4:1.0 to 0.8:1.0 gave various mixtures of desired acid **2a** and the ester formed by condensation with **7a**.