Aroylnitrile Oxide Cyclizations. 1. Synthesis of (3-Aroyl-1,2,4-oxadiazol-5-yl)acetic Acids

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Intermolecular cyclization of 1,3-dipolar aroylnitrile oxides to malononitrile provided a viable approach to a variety of novel (3-aroyl-1,2,4-oxadiazol-5-yl)acetic acid derivatives.

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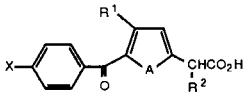
A number of interesting antiinflammatory/analgesic agents including tiaprofenic acid (**1a**) [1], tolmetin (**1b**) [2] and zomepirac (**1c**) [3] have the aroylheteroarylacetic acid framework **1**. As part of our program for developing novel members of this class with improved therapeutic profiles, we sought to prepare the spatially related (1,2,4-oxadiazol-5-yl)acetic acids **2** *via* nitrile oxide cycloaddition methodology.



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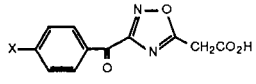


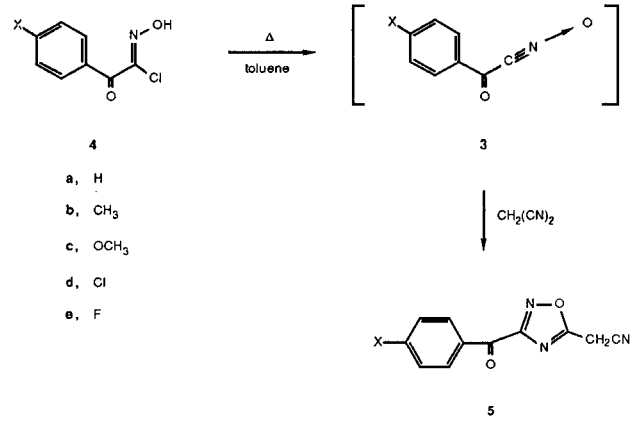
2

	X	A	R^1	R^2
a.	H	S	H	CH_3
b.	CH_3	NCH_3	H	H
c.	Cl	NCH_3	CH_3	H

Reported methodology for the preparation of suitably substituted 5-alkyl-3-aroyl-1,2,4-oxidiazoles is very limited. Brachwitz has converted α-(chloroacetamido)acetophenones to 5-chloromethyl-3-aroyl-1,2,4-oxadiazoles *via* nitrosation [4]. The multistep nature of this method along with the uncertainty of potential cyanation [5] or carboxylation led us to explore a more straightforward aroylnitrile oxide **3** approach [6].

Huisgen has reported on the preparation of a number of 1,2,4-oxadiazoles *via* nitrile oxide dipolar cycloaddition to a variety of nitriles [7]. Although the monoaddition of nitrile oxides to malononitrile had not been previously reported, we felt that the lowered reactivity of this 1,3-dipolar system might allow for the desired chemoselectivity. Indeed, treatment of precursory arylglyoxylohydroxamyl chlorides **4a-e** [8,9] with excess malononitrile in refluxing toluene (method A) provided, in one pot, a variety of nuclear substituted oxadiazoleacetonitriles **5a-e** in modest yields (Table I). The yields of these cycloadditions of aroylnitrile oxides **4** do not appear to be influenced by changes in nuclear substitution.

Scheme I



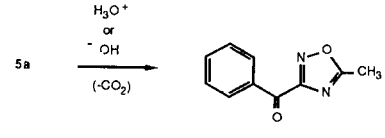
4

a, H
b, CH_3
c, OCH_3
d, Cl
e, F

3

5

The lability of the desired (1,2,4-oxadiazol-5-yl)acetic acids presented a synthetic challenge at this point. Attempted aqueous hydrolysis of nitrile **5a** under standard acidic or basic conditions resulted in concomitant decarboxylation to the 5-methyl-1,2,4-oxadiazole **6**.



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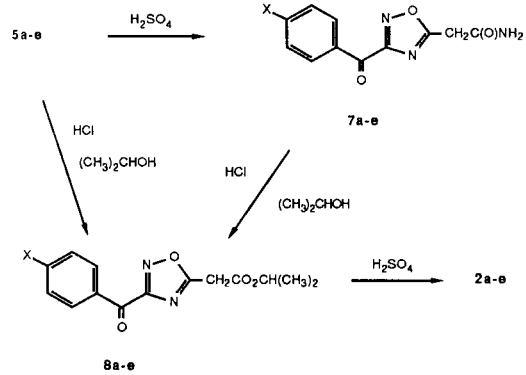
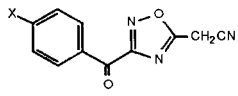
Scheme II



7a-e

8a-e

Table I



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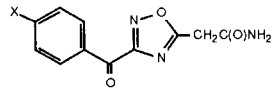

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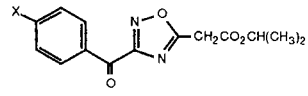
	X	Method	Yield, %	Mp°C	Formula	Analysis Calcd. C	H	N	Found C	H	N
5a	H	A	20	96.5-97.5	$C_{11}H_7N_3O_2$	61.97	3.31	19.71	61.79	3.40	19.57
5b	CH_3	A	19	76-78	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.11	4.10	18.41
5c	OCH_3	A [a]	28	92-94	$C_{12}H_9N_3O_3$	59.26	3.74	17.27	59.25	3.82	17.38
5d	Cl	A [b]	28	81-84	$C_{11}H_6ClN_3O_2$	53.35	2.44	16.97	53.56	2.47	16.64
5e	F	A [c]	32	78-80	$C_{11}H_6FN_3O_2$	57.15	2.62	18.17	56.88	2.73	18.11
7a	H	B	90	155.5-157.5	$C_{11}H_9N_3O_3$	57.14	3.92	18.17	57.17	3.96	18.12
7b	CH_3	B	86	169-171	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.13	58.81	4.52	17.23
7c	OCH_3	B [d]	48	149-150	$C_{12}H_{11}N_3O_4$	55.17	4.25	16.08	55.03	4.32	16.26
7d	Cl	B [e]	71	156-158	$C_{11}H_8ClN_3O_3$	49.73	3.04	15.82	50.14	3.24	15.53
7e	F	B	96	197-199	$C_{11}H_8FN_3O_3$	53.02	3.24	16.85	52.84	3.27	16.98

[a] Purified by hplc using an eluent of 2% ethyl acetate/dichloromethane. [b] 5% Hexane/dichloromethane [c] Dichloromethane. [d] Recrystallized from ethanol. [e] 2-Propanol.

Table II



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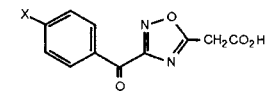

2

	X	Method	Yield, %	Mp°C	Formula	Analysis Calcd. C	H	N	Found C	H	N
8a	H	C	64	oil	$C_{14}H_{14}N_2O_4$	61.30	5.14	10.22	61.59	5.19	10.09
8b	CH_3	C [f]	56	oil	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72	62.60	5.72	9.68
8c	OCH_3	D	73	oil	$C_{15}H_{16}N_2O_5$	59.20	5.31	9.20	59.16	5.36	9.34
8d	Cl	C	71	oil	$C_{14}H_{13}ClN_2O_4$	54.46	4.24	9.08	54.58	4.23	9.19
8e	F	D [f]	80	63-64	$C_{14}H_{13}FN_2O_4$	57.53	4.49	9.58	57.65	4.65	9.49
2a	H	E	48	143-144.5	$C_{11}H_8N_2O_4$	56.90	3.47	12.07	56.86	3.43	12.26
2b	CH_3	E	56	140-141	$C_{12}H_{10}N_2O_4$	58.53	4.09	11.38	58.57	4.25	11.37
2c	OCH_3	E [g]	45	126-127	$C_{12}H_{10}N_2O_5$	54.96	3.85	10.68	54.91	3.89	10.76
2d	Cl	E	56	136-137	$C_{11}H_7ClN_2O_4$	49.55	2.65	10.51	49.90	2.91	10.69
2e	F	E	47	146-148	$C_{11}H_7FN_2O_4$	52.81	2.83	11.19	53.09	2.92	11.25

[f] Purified by hplc using eluent of 15% ethyl acetate/hexane. [g] Purified by trituration with boiling ether.

This problem was circumvented *via* a multistep sequence as seen in Scheme II. Initially, partial hydrolysis of nitriles **5** in concentrated sulfuric acid at room temperature (method B) gave the corresponding amides **7** in good yields (Table I) and this was followed by esterification with anhydrous isopropanol/hydrochloric acid (method C) to result in isopropyl esters **8a,b,d** in yields ranging from 56-71% (Table II). Subsequently, it was found that similar treatment of nitriles **5** (method D) provided esters **8c,e** directly and in higher yields (Table II). Finally, hydrolysis of esters **8** with concentrated sulfuric acid at room temperature (method E) provided the targeted (3-aroyl-1,2,4-oxadiazol-5-yl)acetic acids **2** (Table II).

Compounds **2a-e** displayed activity in antiinflammatory/analgetic screening albeit not as potent as reference compounds such as **1a-c**.

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 PrepLC/System 500 using standard silica gel prepacked cartridges.

Arylglyoxylohydroxamyl Chlorides (**4a-e**).

Compounds **4a-e** were prepared according to a modification of the literature procedure [8,9]. Two equivalents of butyl nitrite was added to a stirred solution of the corresponding α-chloroacetophenones in anhydrous ether while bubbling gaseous hydrochloric acid. The resulting solution was allowed to stand at room temperature overnight.

4-Fluorophenylglyoxylohydroxamyl Chloride (**4e**).

This compound was prepared using the method described above. Workup included concentration, trituration with hexane and recrystallization from carbon tetrachloride to give 85% yield of white crystals, mp 119-120°; ir (chloroform): 3530, 1675 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 6.90-7.40 (m, 2, aromatic H), 7.90-8.30 (m, 2, aromatic H), 12.90 (s, 1, OH); ms: $(MH)^+$ m/e 202.

Anal. Calcd. for $C_8H_5ClFNO_2$: C, 47.66; H, 2.51; N, 6.95. Found: C, 47.67; H, 2.47; N, 7.00.

(3-Benzoyl-1,2,4-oxadiazol-5-yl)acetonitrile (**5a**). Method A.

A mixture of phenylglyoxylohydroxamyl chloride (15 g, 82 mmoles), malononitrile (54 g, 820 mmoles) and 500 ml toluene was refluxed with stirring under nitrogen for 6 hours. The resulting suspension was filtered and concentrated *in vacuo*. The resulting oil was taken up in ether and the organic extract was washed with water (5x) and brine, and dried (magnesium sulfate). Concentration precipitated a solid which was collected and recrystallized from dichloromethane/cyclohexane to give 3.5 g (20%) of an off-white solid, mp 96.5-97.5°; ir (chloroform): 2140, 1675 cm^{-1}; nmr (deuteriochloroform): δ 4.33 (s, 2, CH_2), 7.40-7.90 (m, 3, aromatic H), 8.10-8.50 (m, 2, aromatic H); ms: M^+ m/e 213.

Compounds **6b-e** were prepared similarly and the details are given in Table I.

(3-Benzoyl-1,2,4-oxadiazol-5-yl)acetamide (**7a**). Method B.

A solution of **6a** (5.0 g, 24 mmoles) in 50 ml 98% sulfuric acid was stirred at room temperature overnight. The resulting solution was poured into ice water. The precipitated solid was collected, washed with water and dried *in vacuo* to give 4.9 g (90%) of an off-white powder, mp 155.5-157.5°; ir (potassium bromide): 3390, 1690, 1660 cm^{-1}; nmr (DMSO-d_6): δ 4.22 (s, 2, CH_2), 7.10-8.00 (m, 5, aromatic H and NH_2), 8.10-8.40 (m, 2, aromatic H); ms: $(MH)^+$ m/e 232.

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

Isopropyl (3-Benzoyl-1,2,4-oxadiazol-5-yl)acetate (**8a**). Method C.

A mixture of **7a** (9.2 g, 40 mmoles) and 300 ml anhydrous 2-propanol was saturated with gaseous hydrochloric acid. The resulting mixture was warmed to 70° and maintained there for 11 hours. The resulting cooled mixture was filtered and the filtrate was diluted with water and extracted with saturated sodium bicarbonate and dried (magnesium sulfate). Concentration *in vacuo* gave 10.1 g of an oil. High performance liquid chromatography of 9.8 g of this oil using 20% hexane/dichloromethane as an eluent gave 7.0 g (64%) of a light yellow oil; ir (chloroform): 1735, 1675 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (d, 6, CH_3), 4.14 (s, 2, CH_2), 5.15 (quintet, 1, CH), 7.30-8.00 (m, 3, aromatic H), 8.25-8.60 (m, 2,-aromatic H); ms: M^+ m/e 274.

Compounds **12b,d** were prepared similarly and details are given in Table II.

Isopropyl [3-(4-Methoxybenzoyl)-1,2,4-oxadiazol-5-yl]acetate (**8c**). Method D.

A mixture of **5c** (39 g, 160 mmoles) and one liter anhydrous 2-propanol was saturated with gaseous hydrochloric acid. The resulting solution was refluxed for 5 hours, cooled, poured into cold water and extracted with ether. The organic extract was washed with water (until neutral) and brine, and dried (magnesium sulfate). Concentration and high performance liquid chromatography using 1.5% ethyl acetate/dichloromethane as eluent gave 36 g (73%) of a pale yellow oil that crystallized on standing, mp 63-64°; ir (chloroform): 1735, 1660 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (d, 6, CH_3), 3.90 (s, 3, OCH_3), 4.07 (s, 2, CH_2), 5.10 (quintet, 1, CH), 7.00 (d, 2, aromatic H), 8.35 (d, 2, aromatic H); ms: M^+ m/e 304.

Compound **12e** was prepared similarly and details are given in Table II (See Table II).

(3-Benzoyl-1,2,4-oxadiazol-5-yl)acetic Acid (**2a**). Method E.

Ice-cold 98% sulfuric acid (50 ml) was added to an ice bath cooled flash containing **8a** (8.6 g, 31 mmoles). The resulting mixture was stirred and swirled for three minutes. The resulting solution was poured gradually into ice water. The precipitated solid was collected, washed with water and dried *in vacuo*. Recrystallization from acetone/hexane gave 3.5 g (48%) of colorless crystals, mp 143-144.5°; ir (potassium bromide); 1720, 1670 cm^{-1}; nmr (DMSO-d_6): δ 4.40 (s, 2, CH_2), 7.50-8.00 (m, 3, aromatic H), 8.16-8.50 (m, 2, aromatic H); ms: M^+ m/e 232.

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

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REFERENCES AND NOTES

[1] F. Clemence, O. LeMartret, R. Fournex, G. Plassard and M. Dagnaux, *Eur. J. Med. Chem.-Chim. Ther.*, **9**, 390 (1974).

[2] J. R. Carson, D. N, McKinstry and S. Wong, *J. Med. Chem.*, **14**, 646 (1971).

[3] J. R. Carson and S. Wong, *J. Med. Chem.*, **16**, 172 (1973).

[4] H. Brachwitz, *J. Prakt. Chem.*, **313**, 667 (1971).

[5] R. Jaunin, *Helv. Chim. Acta*, **49**, 412 (1966).

[6] T. Sasaki, T. Yoshiyuki, and Y. Suzuki, *Bull. Chem. Soc. Japan*, **44**, 185 (1971).

[7] R. Huisgen, W. Mack and E. Anneser, *Tetrahedron Letters*, 587 (1961).

[8] N. Levin and W. H. Hartung, *Org. Synth.*, Coll Vol, **3**, 191 (1955).

[9] N. Levin and W. H. Hartung, *J. Org. Chem.*, **7**, 408 (1942).