The Regioselective Synthesis of Tepoxalin, 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-*N*-hydroxy-*N*-methylpropanamide and Related 1,5-Diarylpyrazole Anti-inflammatory Agents

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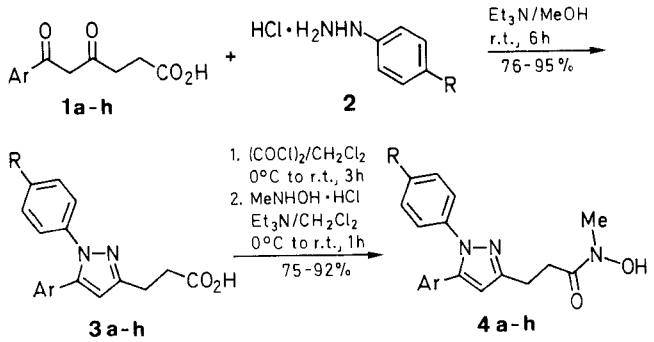
Tepoxalin, a potent anti-inflammatory agent, and its analogs can be synthesized by condensing an appropriate arylhydrazine hydrochloride and a 6-aryl-4,6-dioxohexanoic acid in alcohol with a base catalyst. These diarylpyrazolylpropanoic acids can be converted to their *N*-methylhydroxamic acids by generating the requisite acid chloride, and allowing it to react with *N*-methylhydroxylamine.

Tepoxalin,[1] was synthesized in our laboratories and found to be a potent inhibitor of both the cyclooxygenase and lipoxygenase pathways of the arachidonic acid cascade, as well as a potent anti-inflammatory agent.[2] Herein we are reporting a high yield, regioselective synthesis of tepoxalin and a number of close analogs.

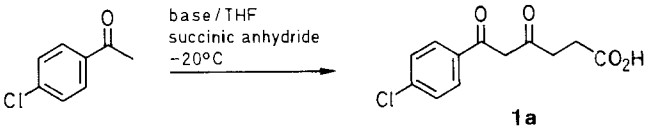
The starting 6-aryl-4,6-dioxohexanoic acids **1** were previously described by us.[3] When these 6-aryl-4,6-dioxohexanoic acids were combined with arylhydrazine hydrochlorides in basic methanol, the desired 3-(1,5-diaryl-3-pyrazolyl)propanoic acids **3** were formed in 76–95% yield. None of the 3-(1,3-diaryl-3-pyrazolyl)-propanoic acids were observed in our lab scale reactions although, in general, when an arylhydrazine is combined with an aryl substituted 1,3-diketone, a mixture of 1,5- and 1,3-pyrazoles results. The 3-(1,5-diaryl-3-pyrazolyl)propanoic acids **3** were then converted to the acid chlorides with oxalyl chloride in dichloromethane. The *N*-methylhydroxamic acids **4** were obtained by adding the acid chloride to *N*-methylhydroxylamine hydrochloride in dichloromethane containing triethylamine. No *O*-acylated hydroxylamine was observed using this method. This method was found to be superior to the standard literature method[5] which utilizes a tetrahydrofuran/water mixture as solvent and always afforded at least trace amounts of the acid **3** as an impurity.



1–4	Ar	R	1–4	Ar	R
a	4-ClC_4H_4	OMe	**e**	3-MeC_6H_4	OMe
b	2-thienyl	OMe	**f**	3,4-$Me_2C_6H_3$	OMe
c	3-pyridyl	OMe	**g**	2-MeC_6H_4	OMe
d	4-MeC_6H_4	OMe	**h**	4-$MeOC_6H_4$	Cl

This synthesis represented an excellent potential manufacturing process for tepoxalin if these reactions could be scaled up to the multikilogram range. Due to the cooling limitations of large equipment it was desirable to carry out the dioxo acid **1** formation at higher temperature than the −78 °C previously described.[3] We found that raising the reaction temperature to −20 °C did not adversely effect the yield of **1a**.

In large scale preparations using commercially available lithium diisopropylamide we noted a small amount of an impurity which was determined to be the diisopropylamide of **1a**. This impurity was present in trace amounts up to several percent depending on the reaction conditions. In an attempt to diminish this impurity we



Base	Yield (%)	Base	Yield (%)
LDA	75	MDA · 1 LiBr	34
LDA · LiCl	< 10	MDA · 2 LiBr	17
MDA	65	LHMDS	85

investigated the effect of the base and the salt load in the enolate forming step. Lithium bis(trimethylsilyl)amide (LHMDS) afforded significantly higher yields with no amide impurity. Magnesium diisopropylamide (MDA) and the lithium chloride loaded MDA and LDA reaction showed reduced yields. On large scale LHMDS is advantageous because, as supplied, it is much less sensitive to air than LDA.

In varying the aryl group on **1a** to generate **1a–d**, we found that at −20 °C with LHMDS we could achieve yields of 78–95% of pure dioxoacids **1a–d** (Table 3).

This synthesis represents a straightforward high yield process for synthesizing tepoxalin and related diarylpyrazolepropanamides.

Table 1. 3-(1,5-Diaryl-3-pyrazolyl)propanoic Acids **3** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS[e] m/z (M + H)
3a	94	126–128 (Et_2O)	$C_{19}H_{17}ClN_2O_3$ (356.8)	2900, 1720	2.7–3.2 (m, 4H), 3.8 (s, 3H), 6.3 (s, 1H), 6.7–7.5 (m, 8H), 8.0 (br s, 1H)	357
3b	86	glass	$C_{17}H_{16}N_2O_3S$ (328.3)	2905, 1720	2.6–3.2 (m, 4H), 3.8 (s, 3H), 6.3 (s, 1H), 6.8–7.4 (m, 7H)	329
3c[f]	76	226–228 (acetone)	$C_{18}H_{17}N_3O_3 \cdot HCl$ (359.8)	3340, 1725	2.7 (t, 2H, J = 7.4), 3.0 (t, 2H, J = 7.4), 3.9 (s, 3H), 7.0 (s, 1H), 7.1 (d, 2H, J = 9.0), 7.5 (d, 2H, J = 9.0), 8.2 (m, 1H), 8.8 (d, 1H, J = 3.5), 9.0 (d, 1H, J = 3.5), 9.3 (s, 1H)	324
3d	95	145–147 (Et_2O)	$C_{20}H_{20}N_2O_3$ (336.4)	2900, 1720	2.3 (s, 3H), 2.8 (t, 2H, J = 8.0), 3.8 (s, 3H), 6.3 (s, 1H), 6.8 (d, 2H, J = 9.0), 7.1 (s, 4H), 7.2 (d, 2H, J = 9.0)	337
3e	95	109–110 (Et_2O)	$C_{20}H_{20}N_2O_3$ (336.4)	2900, 1720	2.3 (s, 3H), 3.0 (dd, 4H, J = 8.0), 38 (s, 3H), 6.3 (s, 1H), 6.7–7.3 (m, 8H)	337
3f	88	141–142 (Et_2O)	$C_{21}H_{22}N_2O_3$ (350.4)	2900, 1720	2.3 (s, 3H), 2.3 (s, 3H), 2.9 (dd, 4H, J = 8.0), 3.8 (s, 3H), 6.3 (s, 1H), 6.7–7.3 (m, 7H)	351
3g	85	111–112 (Et_2O)	$C_{20}H_{20}N_2O_3$ (336.4)	2900, 1720	2.0 (s, 3H), 3.0 (dd, 4H, J = 8.0), 3.8 (s, 3H), 6.2 (s, 1H), 6.6–7.4 (m, 8H)	337
3h	82	glass	$C_{19}H_{17}ClN_2O_3$ (356.8)	2900, 1720	2.8–3.4 (m, 4H), 3.8 (s, 3H), 6.3 (s, 1H), 6.6–7.4 (m, 8H)	357

[a] Uncorrected, measured with a Thomas Hoover apparatus.
[b] Satisfactory microanalysis obtained: C ±0.4, H ±0.4, N ±0.4. Obtained using a Perkin-Elmer 240C element analyser.
[c] Recorded on a Perkin-Elmer 1420 ratio recording spectrophotometer.
[d] Obtained on either a Varian T-60, an IBM WP-100, or a Varian XL-400 NMR spectrometer.
[e] Recorded on a Finnegan MAT 8230 spectrometer as DCI spectra.
[f] Isolated as the monohydrochloride salt.

Table 2. 3-(1,5-Diaryl-3-pyrazolyl)-*N*-hydroxy-*N*-methylpropanamides **4** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS[e] m/z (M + H)
4a	90	125–126 (Et_2O)	$C_{20}H_{20}ClN_3O_3$ (385.8)	3150, 1660, 1610	2.7–3.5 (m, 4H), 3.2 (s, 3H), 3.8 (s, 3H), 6.3 (s, 1H), 6.7–7.4 (m, 8H), 10.7 (br s, 1H)	386
4b	79	glass	$C_{18}H_{19}N_3O_3S$ (357.4)	3150, 1660, 1615	2.2–3.3 (m, 4H), 3.2 (s, 3H), 3.8 (s, 3H), 6.4 (s, 1H), 6.7–7.4 (m, 7H), 10.6 (br s, 1H)	358
4c	75	glass	$C_{19}H_{20}N_4O_3$ (352.4)	3050, 1665, 1585	2.8–3.2 (m, 4H), 3.2 (s, 3H), 6.4 (s, 1H), 6.9 (d, 2H, J = 8.0), 7.1 (d, 2H, J = 8.0), 7.2 (m, 1H), 7.4 (d, 1H, J = 8.0), 8.5 (s, 1H), 8.5 (d, 1H, J = 4.0), 10.6 (br s, 1H)	353
4d	92	119–121 (Et_2O)	$C_{21}H_{23}N_3O_3$ (365.4)	3150, 1650, 1605	2.3 (s, 3H), 2.8–3.1 (m, 4H), 3.2 (s, 3H), 3.8 (s, 3H), 6.3 (s, 1H), 6.8 (d, 2H, J = 9.0), 7.1 (s, 4H), 7.2 (d, 2H, J = 9.0), 10.6 (br s, 1H)	366
4e	82	137–138 (Et_2O)	$C_{21}H_{23}N_3O_3$ (365.4)	3150, 1650, 1605	2.3 (s, 3H), 2.8–3.2 (m, 4H), 3.1 (s, 3H), 3.8 (s, 3H), 6.3 (s, 1H), 6.6–7.3 (m, 8H), 10.6 (br s, 1H)	366
4f	78	130–131 (Et_2O)	$C_{22}H_{25}N_3O_3$ (379.4)	3140, 1650, 1605	2.2 (s, 3H), 2.3 (s, 3H), 2.9–3.2 (m, 4H), 3.1 (s, 3H), 3.8 (s, 3H), 6.3 (s, 1H), 6.7–7.3 (m, 7H), 10.6 (s, 1H)	380
4g	80	117–118 (Et_2O)	$C_{21}H_{23}N_3O_3$ (365.4)	3140, 1650, 1605	2.0 (s, 3H), 3.0 (t, 2H, J = 8.0), 3.2 (t, 2H, J = 8.0), 3.2 (s, 3H), 3.8 (s, 3H), 6.2 (s, 1H), 6.7–7.3 (m, 8H), 10.6 (br , 1H)	366
4h	87	158–160 (EtOAc)	$C_{20}H_{20}ClN_3O_3$ (385.8)	3150, 1660, 1610	2.8–3.4 (m, 4H), 3.2 (s, 3H), 3.8 (s, 3H), 6.3 (s, 1H), 6.6–7.4 (m, 8H), 10.6 (br s, 1H)	386

[a] Uncorrected, measured with a Thomas Hoover apparatus.
[b] Satisfactory microanalysis obtained: C ±0.4, H ±0.4, N ±0.4. Obtained on a Perkin-Elmer 240C element analyser.
[c] Recorded on a Perkin-Elmer 1420 ratio recording IR spectrophotometer.
[d] Obtained on either a Varian T-60, an IBM WP-100 or a Varian XL-400 NMR spectrometer.
[e] Recorded on a Finnegan MAT 8230 spectrometer as DCI spectra.

Table 3. Synthesis of 6-Aryl-4,6-dioxohexanoic Acids **1** with LHMDS at −20°C

Product[a]	Yield (%) (Lit.[4] Value)	mp (°C)[b] (Lit.[4] Value)	Molecular Formula	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR[d] (solvent/TMS) δ, J(Hz)	MS[e], m/z (M+H)
1a	85 (75)	137–139 (137–139)	$C_{12}H_{11}ClO_4$ (254.7)	1705, 1640	$CDCl_3$: 2.7 (m, 4H), 6.1 (s, 1H), 7.5 (d, 2H, J = 8.0), 7.9 (d, 2H, J = 8.0)	255
1b	88 (60)	99–101 (100–101)	$C_{10}H_{10}O_4S$ (226.2)	1700, 1580	$CDCl_3$: 2.8 (s, 4H), 4.1 (s, 0.75, keto), 6.1 (s, 0.75, enol), 7.0–7.4 (m, 3H)	227
1c	78	156–158	$C_{11}H_{11}NO_4$ (221.2)	1650, 1570	acetone-d_6: 2.7 (t, 2H, J = 8), 2.8 (t, 2H, J = 8.0), 6.6 (s, 1H), 7.5 (m, 1H), 8.3 (d, 1H, J = 5.0), 8.7 (d, 1H, J = 5.0), 9.1 (s, 1H)	222
1d	95	139–141	$C_{13}H_{14}O_4$ (234.3)	1713, 2900	$CDCl_3$: 2.3 (s, 3H), 2.7 (s, 4H), 6.2 (s, 1H), 7.3 (d, 2H, J = 8.0), 7.8 (d, 2H, J = 8.0)	235

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.4, N ±0.4. Obtained on a Perkin Elmer 240C analyser.
[b] Uncorrected measured on a Thomas Hoover apparatus.
[c] Recorded on a Perkin Elmer 1420 ratio recording spectrometer.
[d] Obtained on either an IBM WP-100 or a Varian XL-400 NMR spectrometer.
[e] Recorded on a Finnegan MAT 8230 spectrometer as DCI spectra.

All reagents were of commercial quality from freshly opened containers. Magnesium diisopropylamide (MDA) was generously provided by Lithco. All other reagents were available from Aldrich Chemical Co. THF was dried over 4Å molecular sieves and freshly distilled from sodium. Silica gel for chromatography is EM Silica Gel 60, 230–400 mesh.

3-(1,5-Diaryl-3-pyrazolyl)propanoic Acids 3a–h; General Procedure:

A mixture of 6-aryl-4,6-dioxohexanoic acid **1a–h** (20 mmol), arylhydrazine hydrochloride **2** (20 mmol), and Et_3N (2.02 g, 20 mmol) are combined in MeOH (150 mL) and stirred at r.t. for 6 h. The mixture is then concentrated *in vacuo* to a residue which is partitioned between Et_2O (150 mL) and 5% aq HCl (150 mL). The ether layer is separated, washed with 5% aq HCl (2 × 40 mL), and brine (40 mL), dried (Na_2SO_4, 1 g), filtered, and concentrated to a residue. The crude residue is crystallized from Et_2O or acetone to afford the compounds in Table 1. In cases where the compounds do not crystallize they are flash chromatographed on a silica gel column (silica gel 60, 230–400 mesh, 240 g) eluting with hexane/EtOAc/MeOH (50:48:2).

3-(1,5-Diaryl-3-pyrazolyl)-*N*-hydroxy-*N*-methylpropanamide 4; General Procedure:

Oxalyl chloride (1.51 g, 12 mmol) is added to a solution of the acid **3** (10 mmol) in CH_2Cl_2 (100 mL) at 0°C with foaming. The solution was allowed to warm to r.t. and stirred for 3 h. The solution is then concentrated *in vacuo* and redissolved in CH_2Cl_2 (75 mL). This solution is then added dropwise to a suspension of *N*-methylhydroxylamine hydrochloride (1.0 g, 12 mmol) and Et_3N (2.22 g, 22 mmol) in CH_2Cl_2 (100 mL) at 0°C. After addition is complete, the mixture is allowed to warm to r.t. and stirred for 1 h. At this time H_2O (100 mL) is added. The CH_2Cl_2 layer is separated, washed twice each with 5% aq HCl and brine, dried (Na_2SO_4), filtered and concentrated to a residue. The residue is either recrystallized from Et_2O or EtOAc, or chromatographed on silica gel (230–400 mesh, 160 g) eluting with hexane/EtOAc/MeOH (50:48:2) to afford pure **4** (Table 2).

6-Aryl-4,6-dioxohexanoic Acids 1a, b and d; General Procedure:

In a dry, N_2 filled, round-bottomed flask fitted with a stirrer and addition funnel, lithium bis(trimethylsilyl)amide/heptane solution (1.1 M, 125 mmol, 113.6 mL) and THF (200 mL) are added and the solution is cooled to −20°C. To this solution is added slowly (over 5 min) a solution of aryl ketone (125 mmol) in THF (100 mL). The resulting solution is stirred at −20°C for 30 min. To this solution is added a solution of succinic anhydride (5 g, 50 mmol) in THF (200 mL). The solution is stirred for 1 h at −20°C and allowed to warm to r.t. and stirred overnight. At this time, 3N aq HCl (100 mL) and Et_2O (500 mL) is added. The layers are separated, and the Et_2O/THF layer is extracted with 1N NaOH (2 × 100 mL). The base extracts are combined, acidified to the cloud point (approx. pH 2) with 3N aq HCl, the precipitate which forms is collected by filtration and dried under high vacuum. Alternatively, extraction with CH_2Cl_2 (2 × 250 mL) at the cloud point, followed by drying (Na_2SO_4), filtration, and concentration to a solid residue affords similar yields to precipitation. Recrystallization from Et_2O or acetone affords the compounds described in Table 3.

4,6-Dioxo-6-(3-pyridyl)hexanoic Acid (1c):

LHMDS (1.1 M in heptane, 91 mL, 100 mmol) is dissolved in THF (250 mL) and cooled to −20°C. 3-Acetylpyridine (12.1 g, 100 mmoles) in THF (50 mL), is added at once. After 2 min a gel is formed and the reaction vessel is then moved to a sonicator and sonicated for 10 min at 0°C. At this time succinic anhydride (4 g, 40 mmol) in THF (50 mL) is added at once. Sonication is continued for 30 min at 0°C. Et_2O (50 mL) and H_2O (150 mL) are added. The H_2O layer is separated and acidified to pH 6.5 with 1N aq HCl at which point a precipitate forms. The solid is filtered, dried under high vacuum and recrystallized from acetone to afford **1c**.

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